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FISCAL
YEAR
1981

ANNUAL
REPORT

VOLUME 1

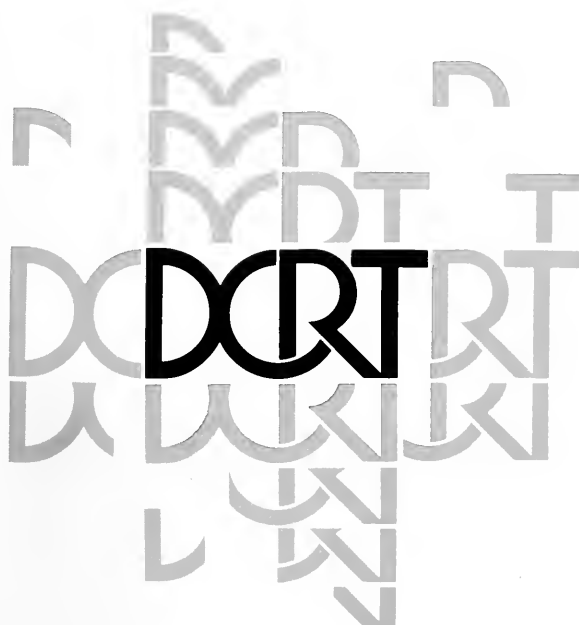


DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

FISCAL
YEAR
1981

ANNUAL
REPORT

VOLUME 1



Foreword

The work of the Division of Computer Research and Technology covers a large spectrum of activities. It ranges from doing research in biology, statistics, mathematics, and computer science to providing computer facilities and services for the NIH.

The several DCRT laboratories and branches embody and integrate this variety of talents. Each has a major functional focus. But the success of the Division's work arises from the interaction of members of each group with others across organizational and disciplinary lines. Many projects in the Division require the expertise of people from several segments of the spectrum.

DCRT's collaborative projects link its staff to professionals both inside and outside NIH. The result is a balance in emphasis to provide the work done by DCRT at NIH with the benefits of collaborations outside of NIH.

While DCRT does not have money for grants, it does provide occasional support for meetings on scientific topics related to its work.

This year's annual report is presented in two volumes:

Volume 1 gives a summary overview of the work of each group and highlights its accomplishments.

Volume 2 includes detailed projects and activities of each group.

If you have comments on the report or suggestions for improving future annual reports, please send them to:

DCRT Information Office

Building 12A, Room 3027

Division of Computer Research

and Technology

National Institutes of Health

Bethesda, Maryland 20205



Dr. Arnold Pratt, DCRT Director, is internationally known for his research in computational linguistics.

From the Director

The Division of Computer Research and Technology (DCRT) was established in 1964 to make computers useful at NIH. Over the years, the work of the Division has become an integral part of the conduct and management of NIH research programs.

It is a pleasure to report once again the accomplishments of the people in an exceptionally competent and productive group of laboratories, branches, and offices. All parts of the DCRT program are important for that balance of science and technology that has made the Division and computing throughout NIH so successful.

Three brief glimpses into the stream of fiscal year 1981 history help to show that computing thrives and supports progress in all the NIH programs.

- NIH biomedical scientists got wide recognition for using computers. A single June issue of the *NIH Record* carried three examples.

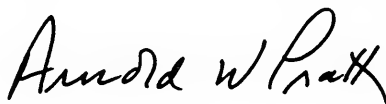
One article told of a young NIH staff physician becoming professor of radiology at an academic medical center. He first came to NIH in 1973 as a medical student for our course on computers in medicine; after graduating, he returned to work in DCRT and in the NIH Nuclear Medicine Department, creating and using new computing techniques.

Another reported an award by the Endocrine Society to an NIH medical scientist for outstanding leadership and service. The award was for his development of a series of computer programs that are used in laboratories throughout the world as well as widely at NIH.

The third story told of a prestigious European prize for distinction in advancement of knowledge about diabetes mellitus. The picture in the *Record* showed the recipient working at a computer terminal, using one of the several advanced DCRT systems he exploited successfully while he was a Visiting Scientist at NIH.

- NIH can pay its suppliers promptly. A computer system can now process vouchers for goods and services as soon as they come to the NIH Accounts Payable Section. In the past, manual processing labored under week- or month-long backlogs. The administrative data base system created by DCRT staff cuts out most of the paper work in voucher payment, and it also automatically records obligations and accruals in the central accounting record.
- The NIH Computer Center obtained contracts for new equipment. This feat came after seemingly endless years of preparation and negotiation. Over the next five or more years, the 8,000 users of the central NIH systems will benefit in a timely way from proven advances in computing technology.

DCRT looks forward with enthusiasm to the coming year as an opportunity to work with NIH scientists and administrators in creating still more powerful and useful systems. The challenge lies in building strong intellectual links from computers, mathematics, and engineering to the substance of science and the art of administration. After 17 years the frontiers of computing remain open for new advances in all NIH programs. Research and development programs within DCRT will continue to help lead the way.



Arnold W. Pratt, M.D.

Director

Division of Computer Research
and Technology

Contents

Division of Computer Research and Technology

Laboratory of Statistical and Mathematical Methodology 8

Provides statistical and mathematical help in the computer analysis of biomedical data; offers statistical and mathematical packages for users; develops methodology in multivariate analysis, curve fitting, biological shape and pattern theory.

Computer Systems Laboratory 14

Provides consultation and collaboration in the design and implementation of specialized computer systems for laboratory and clinical applications.

Laboratory of Applied Studies 20

Relates mathematics, statistics, and computer science to such biomedical problems as ECG analysis, evaluation of physiological systems in health and disease, modeling of the microcirculation, and estimation problems in laboratory medicine.

Physical Sciences Laboratory 24

Conducts research in mathematical theory and practical instrumentation to explain biological phenomena in terms of chemistry and physics at the subcellular molecular levels.

Data Management Branch 28

Serves as a central resource of systems analysis, design, and programming for data processing projects relating to scientific, technical, management, and administrative data.

Computer Center Branch 32

Designs, implements, and operates the NIH Computer Center; provides assistance, training and technical communications to the more than 8,000 users of the Central Utility.

Office of ADP Policy Coordination 39

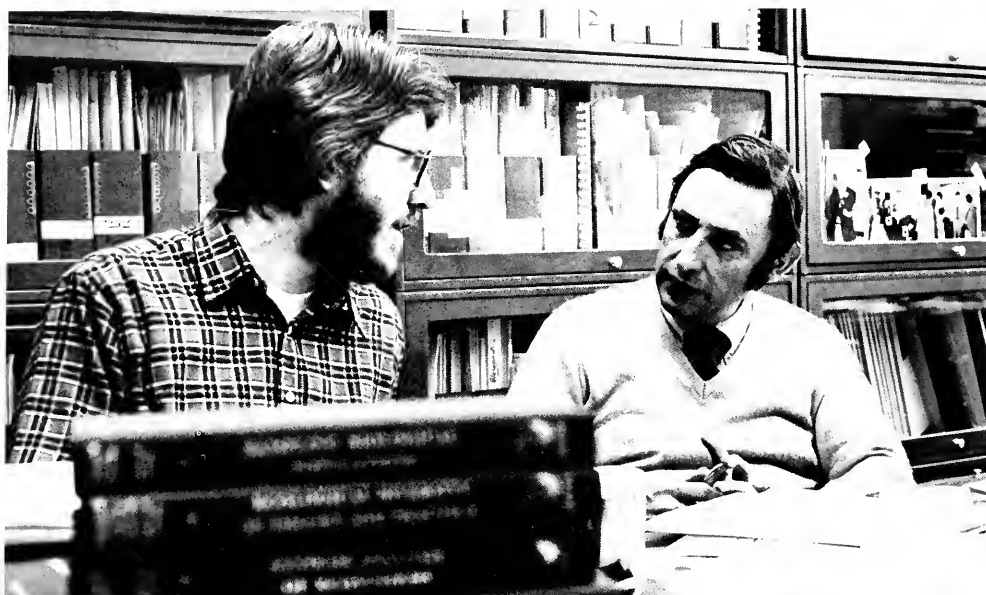
Coordinates the complex Federal policies and procedures that govern getting and using computers at NIH.

Office of Administrative Management 41

Provides general administrative management support for the Division's work.

Office of Scientific and Technical Communications 42

Serves as a central source of information about DCRT activities and about computer-related disciplines.



LSM combines research in mathematical statistics, mathematics, and computer and information science.

Research projects in LSM vary from studies of natural language processing for medical information systems to studies in statistical methodologies for biomedical applications.



Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

Function

The Laboratory of Statistical and Mathematical Methodology (LSM) combines research in mathematical statistics, mathematics, computer, and information science with collaboration and service in these areas to NIH researchers and administrators.

In addition to the position of chief, the laboratory has fifteen full-time professional positions distributed among four sections:

- The **Statistical Software Section (SSS)** provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis, including selection and support of large systems/packages. Three specialists in scientific programming are led by a computer systems analyst whose specialty is statistics.
- The **Biomathematics and Computer Science Section (BCS)**, directed by a mathematician, performs independent research and provides consultation and collaboration in the specialties of its five computer and mathematical scientists.
- The **Statistical Methodology Section (SMS)** works closely with the Statistical Software Section. Two professionals in mathematical statistics provide biostatistical consultation and do independent research.
- The **Medical Information Science Section (MIS)** investigates and develops methods for application of information and computer science to medical language data processing. Two computer specialists work under the direction of a computer systems analyst who is an expert in computational linguistics.

Scope of Work

LSM staff interact with all NIH institutes, with other Federal agencies outside HHS, and with biomedical researchers worldwide. FY81 was LSM's seventh year as a separate entity within DCRT. The volume of its computational and consultative services continued to expand; its research activities maintained about the same level as the preceding year.

A major part of LSM activity is the offering of statistical and mathematical systems/packages to the NIH user community. LSM accepts responsibility

for evaluation of new systems/packages and their suitability for NIH. When it offers a system/package to the NIH community, LSM makes three basic commitments:

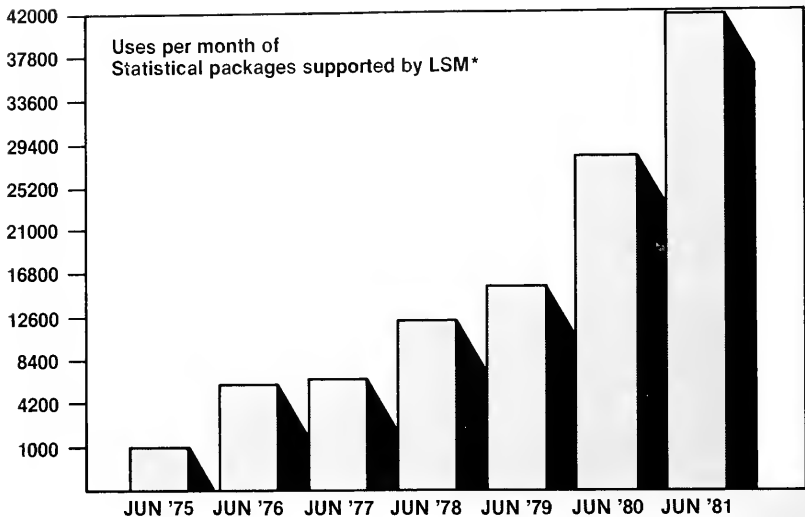
1. Maintenance of the package, with adequate documentation, through NIH computer system changes, system/package updates, and corrections.
 2. Rapid response to queries concerning user access to a system/package program, including job control language and program parameters.
 3. Assistance in interpretation of results.
- During this year, as in the past year, the Statistical Software Section of LSM maintained the following systems/packages and programs on the IBM 370 system of the DCRT Computer Center:

BMD (BMDP, Biomedical Computer Programs, UCLA)
SPSS (Statistical Package for the Social Sciences, SPSS, Inc.)
SAS (Statistical Analysis System, SAS Institute, Inc.)
P-STAT (Statistical Package, P-STAT, Inc.)
IMSL (International Mathematical and Statistical Libraries, IMSL, Inc.)
MSTAT1 (Collection of Mathematical and Statistical Programs, DCRT)

There is a major commitment to maintain these systems/packages and respond to queries about their use. In FY81 alone the SSS staff responded to over 4,500 calls. Also during this year, every system/package went through at least one major update.

The Biomathematics and Computer Science Section maintains several systems/packages and specialized systems on the DECsystem-10 of the Computer Center. Foremost in use is the interpretive system MLAB, designed (by LSM scientists) for biomathematical modeling. BCS supports the PROLOG system (for non-numerical data processing) and also a DECsystem-10 version of IMSL whose S/370 version is supported by SSS. C-LAB, a system on the DEC-10 for pattern recognition and clustering (written by an LSM scientist) is supported by SMS. The Unified Generator Package, written and maintained by a BCS staff member, is on DCRT's IBM System 370.

As a result of LSM's policy of not only supporting the use of these systems/packages but also aiding in



*Packages supported by the Statistical Software Section only. Does not include packages supported by the Biomathematics and Computer Sciences Section.

the interpretation of their output, the statisticians of the Statistical Methodology Section provide consultation over a wide range of scientific fields. Some very brief consultations are very successful because there is a known answer to the question at hand. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

Research projects in LSM vary widely from studies of natural language processing for medical information systems and studies of efficient algorithms for information retrieval to studies in mathematics and statistical methodologies for biomedical applications.

Highlights of the Year's Activities

Computation

In FY81 LSM continued to expand teaching and documentation for supported systems/packages. LSM taught four introductory courses for SAS, two for BMDP, two for SPSS, and one for IMSL. In addition, two introductory courses and one advanced course for MLAB, and one introductory course for C-LAB were taught. Five articles on MLAB techniques and one article on mathematical modeling of chemical kinetics systems appeared in *INTERFACE*. A new edition of the *MLAB Applications Manual* was released, with additional sections on bivariate density analysis (including 3-dimensional graphics and contour mapping methods in MLAB) and on delta modulation encoding of signals.

Two new systems/packages were offered on an experimental basis to the NIH computer user community. SCSS, an interactive version of SPSS, and SAS/GRAPH, a graphics package from the SAS Institute, were installed and tested at DCRT.

A DECsystem-10 utility program for interactive computer generation of an index to a user's document was completed. It is being production-tested on new editions of the *MLAB Reference Manual* and the *MLAB Beginner's Guide*, now in preparation.

MLAB was enhanced by technical improvements to increase speed and reduce memory requirements and by the addition of Fourier transform and inverse transform operators.

Consultation, Collaboration, and Research

As in FY80, LSM consultation and research in FY81 was closely tied to the use of the computer. Most consultations (55 percent) involved statistical advice combined with considerable computer use. Others (40 percent) involved computer use alone and a small fraction (5 percent) involved mathematical or statistical advice with only limited computer use.

In FY81, LSM research, collaborative, and consultative efforts merged more closely and were less distinguishable among themselves. In a number of studies, statistical methodologies were developed for, or modified to suit, specific biomedical problems. For example, in a collaboration with A. DeBlas, NHLBI, discrete distribution models were used to

analyze data from monoclonal hybridoma experiments. In a collaboration with A. Grimes, CC, an unordered paired-data method was modified to study monaural versus binaural amplification in hearing-impaired children. In a third example, a collaboration of several years duration (with Drs. G. Hirschman, R. Wineman, and M. Wolfson, NIADDK) on complications of dialysis for patients with end stage kidney disease was completed, using a special method for adjusting hospitalization rate by the patient's length of time at risk. Results from all three collaborations have been published or accepted for publication.

Other areas in which LSM consultation led to productive collaborative efforts include studies on schistosomiasis with Dr. A. Cheever, NIAID, with three papers published, as well as studies on the pain syndrome Causalgia with Dr. A. Tahmouh, NINCDS. In the latter case a paper, using linear model methods, for unbalanced data, has been prepared on measurements of sympathetic nervous system activity in patients versus controls.

Statistical research on simultaneous confidence intervals for ratios continued in FY81. The results, of wide applicability, are accepted for publication. Other research included a study of the connection between statistical and algebraic independence. These results are applicable to the sample covariance matrix of multivariate data. This latter is important in statistical discriminant analyses, which is a subject of LSM research in collaboration with Drs. J. Darroch, Flinders University, South Australia, and H. Hoffman, DRS. Discriminant methods adapted for size and shape variables are being used to study genetic variation in laboratory mice. A separate study of independence of size and shape variables before and after scale change is in press, along with other LSM studies of statistical distributions.

In computer science, research on computer generation of scientific manuscripts led to development of an interactive software system. This system has the capability of generating complex displays of mathematical formulas and MLAB graphics on a high-resolution printer-plotter. Recent research on procedures for managing extendible array files was completed and published. Research also continued on the 'symmetric axis' method for



Staff members teach courses on the use of various program packages that LSM supports.

The Statistical Software Section (SSS) provides consultation to and collaboration with NIH researchers and administrators.



describing biological shapes. This included augmentation of software, publication of a paper on the geometry of the three-dimensional case, and collaboration with Dr. R. Webber, NIDR, in the analysis of human mandible images. Mathematical studies of equivalence of theories of modules over ring, and also of convex homogeneous cones in finite-dimensional vector spaces over the real field were completed. The latter studies have potential application in a variety of areas, including size and shape variables. In linguistic analysis an extensive set of IBM 370 assembly language programs was developed for the automatic identification of prefixes and suffixes in French medical terminology. In collaboration with Drs. J. Costa and D. Henson, NC studies of the automatic processing of natural language surgical pathology reports continued.

Future Plans

No major shift in laboratory service or research is anticipated in the coming year. Current levels of statistical and mathematical systems/packages support, consultation, and user assistance will be maintained. Research projects will be continuations of those already initiated and reported here.

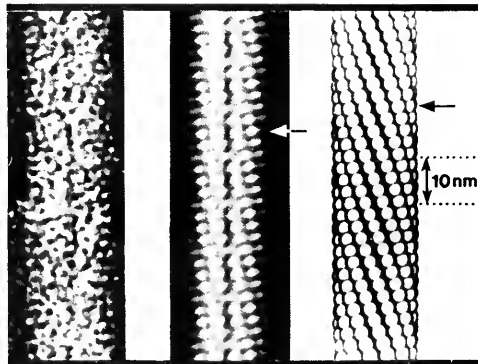
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Harold Ostrow, a CSL engineer, contributed to the development of the heart probe, which allows non-invasive study of cardiac function.

Dr. Benes Trus (CSL) and Dr. Alasdair C. Steven (NIADDK) collaborated to study the molecular organization of beet necrotic yellow vein virus (Virology, in press). Left: original electron micrograph; middle: computer reconstruction; right: computer model.



Function and Scope of Work

The Computer Systems Laboratory, a group of about 30 professionals representing the disciplines of engineering, computer science, medicine, and chemistry, is the major source of expertise at NIH for minicomputer and microcomputer technology. CSL engineers and scientists, in collaboration with NIH laboratory and clinical investigators, apply this technology in the areas of laboratory automation and patient care. Most work supports intramural research programs, although some projects have been undertaken with extramural programs and, more rarely, with other Federal agencies. In addition to supporting ongoing research, CSL also investigates new applications of computers to biomedical research and identifies appropriate technology for use in these applications.

Small computers that can be used in the laboratory or at the patient's bedside are increasingly important to biomedical and clinical research because of more complex research methods and instrumentation. Laboratory automation, data acquisition from analytical instruments, and patient monitoring are examples of functions to which CSL has applied small computers at NIH. Computers may be used only in an adjunctive manner, for example, as a more convenient means to acquire laboratory data; or they may be integral parts of an elaborate instrumentation system such as the computer-controlled mass spectrometer.

Recent technological advances are contributing to changes in the nature of CSL's work. Foremost among these advances are developments in large scale circuit integration (LSI)--the microprocessor revolution--that have brought about the miniaturization of computer components and a dramatic decline in their prices and power requirements. One result has been a greater availability of computers for biomedical research. Thus, CSL engineers are now able to use microprocessors to solve problems that once were avoided because of cost, size, or manpower constraints.

The Laboratory brings together professionals with diverse backgrounds to apply computer technology effectively to NIH programs and to offer research and development capabilities responsive to NIH needs. Engineers, computer scientists, and

mathematicians evaluate and apply new electronics and computer technology to solve biomedical problems. Personnel with backgrounds in medicine, biology, and chemistry communicate effectively with biomedical investigators and clinicians and identify potential computer applications. This multidisciplinary approach aids the recognition of problem areas that will benefit from automation and the interpretation of research needs in terms of computer methods.

This year, CSL engineers and scientists worked on approximately 28 projects, representing collaboration with almost all of the Institutes. Many of these projects were continued from previous years; 9 projects were begun this year and there were significant changes in scope in four others. Projects range in size from consulting activities of a few days or weeks duration to large scale efforts taking a number of man-years. Because much work involves the development of new methods or technology, or is influenced strongly by the changing needs of research, it is often difficult to predict the long term scope of a project.

Fiscal Year 1981 Highlights

During the past year the scope of CSL computing has broadened considerably. Modest computing requirements posed by individual scientists, or local groups of investigators, are being met increasingly through the use of microcomputers, while at the other end of the computational spectrum CSL is involved in the design, development, and management of large minicomputer systems, including, for example, those directed toward providing general image processing services to a significant segment of the NIH community.

Two projects that typify the exploitation of microcomputer technology in clinical and laboratory settings are, respectively, the Automated Pulmonary Physiology Testing Project and the Molecular Interaction Laboratory Data System. The Automated Pulmonary Physiology Testing Project utilizes a Digital Equipment Corporation DECLAB MINC 11/03 microcomputer system in support of pulmonary dysfunction diagnostic testing. Analog signals are rapidly acquired, digitized, and analyzed, providing the physician with intermediate results that can be

used to determine the course of further testing. Reports suitable for the medical record are produced locally and, together with any raw data desired, archived in machine readable form for retrospective analysis. These data will eventually be incorporated into the Pulmonary Branch data base being developed by DCRT's Data Management Branch on the NIH IBM 370 computers. Telephone data transmission to either the IBM 370 or the DECsystem-10 computers of the NIH Central Facility will then afford the Pulmonary Laboratory offline access to a full array of scientific, mathematical, and database manipulation functions. Specific procedures already implemented include static compliance and inspiratory muscle strength. Treadmill stress testing, dynamic compliance, and work of breathing are currently being added to the system repertoire. Future plans anticipate the establishment of breath-by-breath studies and closed-loop exercise procedures where such parameters as patient heart rate may be held constant by varying treadmill speed and grade. Use of this system has resulted in decreased time and increased accuracy and quality of the procedures performed, thus benefitting patient and physician alike.



CSL collaborative efforts put minicomputers and microcomputers to work for a variety of scientific needs throughout NIH.

The recently completed Molecular Interaction Laboratory Data System features a Digital Equipment Corporation PDP-11/03 microcomputer system interfaced to a Beckman Model E analytical ultracentrifuge and a Cary Model 61 circular dichroic spectropolarimeter owned by the Molecular Disease Branch, NHLBI. Ultracentrifuge data are conditioned, converted, formatted, and graphically displayed on a

video display terminal. A system operator selects data for further processing and creates a file from these data, and from data required for analysis functions that have been previously entered into a log file. This file of preprocessed data is then transferred to the NIH DECsystem-10 where preestablished command sequences, invoked under the modeling laboratory program MLAB, are used to compute molecular weights and to assess molecular interactions. Circular dichroism spectra generated by the Cary 61 spectropolarimeter are digitized and high frequency noise is removed by digital filtering techniques. Spectra may be added, subtracted or averaged prior to transfer to the NIH DECsystem-10 for further analysis. Typically the samples analyzed by this technique are proteins that the investigator wishes to characterize with respect to their three-dimensional conformations under various conditions. Using recently published data on the relationship between circular dichroism spectra and conformation in terms of the contributions to its structure by the four basic types of tertiary structure: helix, beta sheet, beta turn, and random coil.

A significant increase in computational complexity over that represented by microcomputer projects is found in long-term CSL support for the flow microfluorimetry/cell sorter users at NIH. This work started as a minicomputer-based project to acquire, display, and analyze data from a Becton-Dickinson flow microfluorimeter (FMF) and a Los Alamos Scientific Laboratory FMF. Successful system development and operation has led to reproduction of the system for a number of new users and to incorporation of microcomputer technology to meet expanded requirements. The basic minicomputer system is implemented on a Digital Equipment Corporation (DEC) PDP-11/34 computer and features CSL instrument interfaces and an extensive software package that runs under DEC's single user RT-11 operating system. During the past year a system was installed for NHLBI and two were installed for NCI, thus bringing to five the number of systems supported by CSL. Copies of the CSL design are also being used by several organizations outside of NIH.

To facilitate the simultaneous acquisition and processing of FMF/cell sorter data in a high workload environment, development is underway to replace the DEC RT-11 operating system with the

DEC RSX-11M multiuser operating system. An LSI-11 microcomputer is being introduced into the system to remove the data acquisition task from the PDP-11/34 computer. Besides providing independent operator interaction during parameter entry and acquisition phases, the microcomputer will produce a permanent hardcopy of the 'laboratory notebook.' It is planned that only completed data files will be transferred across the direct memory access link between the LSI-11 microcomputer and PDP-11/34 computer.

An increasing number of scientific projects at NIH produce visually-based experimental data such as electron micrographs, stained tissue sections, gel electrophoresis, autoradiographs, etc., which require objective, accurate, quantitative analysis. Utilizing DCRT's powerful DEC PDP-11/70 -driven Evans and Sutherland Image Processing System as the key resource, CSL has, for the past three years, collaborated with scientists of several Institutes in a variety of image processing projects. Although these projects were directed toward specific goals, an important supplementary aim was the creation of general purpose software easily adaptable to a wide range of image processing needs. This latter role has expanded significantly during FY81 as CSL was assigned a major role in managing the Evans and Sutherland Image Processing System.

Current CSL involvement with the Evans and Sutherland Image Processing System is focused primarily on the development of biomedically-oriented image processing software, complemented by the support necessary to make such packages usable to NIH scientists. Typical programs included PIC, CINT, and MONKEY. The PIC software package facilitates examination of collagen structure from electron micrographs, performs quantitative analysis of one-dimensional gels, and elucidates virus structures. CINT automatically locates and integrates up to 1200 spots on a two-dimensional gel picture and provides limited analysis of autoradiographs. MONKEY is a general image enhancement package that can be used to evaluate all or part of an image and includes operations such as smoothing, sharpening, statistics, and linear combinations. The Evans and Sutherland System supports both molecular graphics and image processing users. Demand upon the system has escalated to such a degree that severe scheduling problems exist not

only during prime time but throughout most of the evening period as well. Many image processing problems, moreover, are not amenable to solution on the powerful but relatively dated Evans and Sutherland System. CSL is therefore in the process of designing and procuring a new image processing system. This system will consist of a powerful 32-bit computer with a mixture of medium and high resolution video displays. The microdensitometer associated with the Evans and Sutherland System will not be required by molecular graphics users and will be used to provide precise digitization of x-rays, micrographs and other images. The computer and its peripherals have been purchased and delivery is anticipated in FY82. Procurement of the display subsystem is being held up pending the availability of funds.

Continuing in its more traditional role CSL has pursued a number of collaborative image processing projects. A new project, undertaken with scientists from the NEI and Harvard Medical School, is track cataract disease history. Images produced by split-lens lamp photography are digitized by means of microdensitometry and entered into the computer



CSL engineers and scientists evaluate and apply electronics and computer technology to solve biomedical problems.

concerned with measurement of opacity of the human eye lens along the visual axis in order to for analysis. Present work is oriented to determine the effects of variables--such as camera type, photographer, photographic processing, and microdensitometry factors--on experimental accuracy.

Another project new this year focuses the combined power of Computer Assisted Tomography (CAT) and Positron Emission Tomography (PET) upon a study of brain cell metabolism and its relationship to disease associated with aging. Conducted in conjunction with NIA scientists, the project's initial goal is to delineate brain substructures represented in sequential CAT scan images and to determine metabolic activity in these substructures from corresponding sequential PET scan images.

Ongoing image analysis work with the NHLBI includes topographic analysis of arterial atherosclerosis formation and graphical representation of myocardial blood flow. Further refinement of the block model used by NINCDS scientists to provide three-dimensional graphic representation of the neuronal structure of the cat brain stem now make it useful for arbitrary plane viewing of other spatially-sequenced images.

Good R & D programs require good tools. For many years CSL has had an electronics laboratory. More recently, a computer laboratory has been added. The computer laboratory facilities include 'development systems'--minicomputer and microcomputer systems--that are used to investigate and implement new software and hardware for eventual use in target computer systems, i.e., systems intended for use in specific projects. These development systems permit work to begin on a project long before the target system ordered for that project is delivered, thus improving productivity and reducing the time until project completion. Development systems are indispensable to microprocessor projects, because software development work is often not possible on the microprocessor hardware itself. The computer laboratory facilities were expanded again this year so that more people can use the development systems at the same time. Virtually all minicomputer and microcomputer work can now be done using development systems.

CSL is called upon for consultative assistance in its areas of expertise by both the intramural and extramural programs. Usually such assistance is limited to providing expert advice--the conventional definition of consulting. Occasionally however, a consulting role may lead to engineering or software work, or even to an extensive project. During the

past year consultation activities with the Rehabilitation Medicine Department of the Clinical Center led to a survey of the state-of-the-art in gait laboratory automation. Subsequent to this survey, requirements, possible design approaches, and costs for automating the NIH Gait Laboratory were studied. A collaborative project culminating in the computerization of NIH Gait Laboratory activities appears imminent.

The Computer Systems Laboratory continued its support of the annual international conference, Computers in Cardiology. This conference provides a forum for direct interaction and exchange among physicians, computer scientists, and engineers who use computers to assist research or clinical care in the field of cardiology.

Future Plans/Trends

In common with many organizations, CSL can expect FY82 and beyond to be clouded by many of the uncertainties that were encountered this year concerning resources. Technological developments in large scale circuit integration promise an increase in the number of biomedical applications for which microcomputers and minicomputers can be useful and affordable; however, anticipated budget reductions combined with an unpredictable rate of inflation may well offset these advances. The proposed new Image Processing System poses a striking example of the potential conflict. Hailed just one year ago as a project that owed its feasibility to technological progress and declining costs, it has remained virtually dormant during the past year, a hostage to the unavailability of funds.

An expected continuation of stringent personnel restrictions serves to further obscure a precise forecast of future directions. Limitations in staffing tend to encourage an escalation in demands for automation; however, all new NIH computer initiatives will have to be reconciled with uncertain funding and uncertain CSL support. Moreover, CSL has for many years required Institutes to provide some limited computer expertise as a condition for assistance. At a time when CSL is fully extended, the commitment of Institute personnel assumes greater than usual significance; participation by the Institutes will prove difficult as so many computer

projects permit increasingly complex research activities rather than conserve manpower. An excellent illustration of staffing problems can be seen in the NIH Library Project. Automation of the Library has become imperative if an exploding volume of literature is to be managed by a fixed or shrinking Library staff. Nevertheless, after languishing for one year in a CSL project queue awaiting the availability of appropriate personnel, the project has suffered another equally lengthy delay due to the existence of a similar staffing plight in the NIH Contracts Department.

The substantial uncertainties and delays that have plagued many recent projects make effective use of a limited CSL staff an imposing challenge. A number of actions adopted to confront the resource problems appear to hold promise and may become trends for the future.

A contract to provide software support has been established and already two projects are expected to benefit from this type of support. Provided that adequate funding can be maintained, the contract mechanism offers an attractive supplement to CSL programming capability, particularly for well defined projects.

As was the case during the past year, continued heavy involvement in providing consultation services can be expected for the future. During the past year, for example, substantial specialized advice was given to the National Toxicology Program, NHLBI Framingham Longitudinal Study, Clinical Center Department of Critical Care Medicine, Clinical Center Nuclear Medicine Department, NHLBI Surgery Branch, NHLBI Cardiology Branch, Clinical Center Department of Rehabilitation Medicine, and NCI Surgery Branch. Although some consultations have been, and undoubtedly will continue to be, substitutes for actual work on indefinitely delayed projects, consultation services can offer, in appropriate circumstances, substantial rewards relative to limited personnel investment.

Finally CSL will continue to deploy staff on those projects promising maximum impact to the NIH Community. Current examples of this policy are the Flow Microfluorimetry Project with its duplicated systems and the Image Processing Project with its general purpose developments.

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In collaboration with the NIH Nuclear Medicine Department, LAS researcher Margaret Douglas is producing diagnostic images (see insert) that allow scientists to detect motion defects in the walls of the heart.



Special Achievement Awards were earned by Martha Horton and Margaret Douglas for their contributions toward developing a text- and command-entry technique for computerized typesetting printing systems. The awards were presented by Dr. Eugene Harris, Chief, LAS.

Laboratory of Applied Studies

Eugene K. Harris, Chief

Functions

The Laboratory of Applied Studies (LAS) has three main purposes:

1. in collaboration with biomedical scientists, to apply mathematical theory and computing science to the construction, testing, and improvement of mathematical models of physiological processes--particularly reaction-diffusion kinetics, transport of substrate to tissues, and the control of metabolism within cells and tissues;

2. in collaboration with clinicians, to develop and apply mathematical or statistical theory and special-purpose computing procedures (analog or digital as required) to facilitate research projects aimed at improving the diagnosis of disease and assessment of treatment;

3. to engage in independent research in applied mathematics, statistics, and computer systems necessary to provide a sound theoretical basis for collaborative studies, and to insure that state-of-the-art mathematical and computational methods are available as research tools at NIH.

Two sections carry out these primary LAS functions:

Applied Mathematics Section--AMS--(John E. Fletcher, Ph.D., Chief). This staff of five includes specialists in applied mathematics, computer science, biomathematics, and medicine.

Medical Applications Section--MAS--(James J. Bailey, M.D., Chief). This five-member staff includes physician-scientists, electronic engineers, and computer systems analysts.

The Chief, LAS, is a biostatistician with training in public health and the basic medical sciences.

Scope of Work

The Laboratory of Applied Studies works on projects in basic and clinical biomedical science. Largely, these involve collaboration with other groups at NIH, elsewhere in the U.S.A., and abroad. The collaborating investigators this year included:

- *biochemists and pharmacologists* at NIH, at the Medical College of Virginia, and at other universities in the U.S.A. and in France working on models for receptors of drugs or other ligands, on the kinetics of enzymes in membranes and on other problems in tissue metabolism

- *physiologists and chemical engineers* in the U.S.A and Europe studying the transport of substrate within the microcirculation and the regulation of tissue perfusion
- *clinicians* in the cardiology, pulmonary, and hematology branches of the NHLBI; in the arthritis and rheumatism branch of the NIADDK; and in the medical intensive care unit and the departments of diagnostic radiology and diagnostic imaging of the Clinical Center
- *clinical chemists and pathologists* at NIH (Clinical Pathology Department, Clinical Center) and elsewhere in the U.S.A., in Europe, and in Japan engaged in the collection and study of reference values in laboratory medicine
- *electrocardiologists and biomedical engineers* in the U.S.A., Canada, and Europe concerned with improved algorithms for computer-based interpretation of ECG's and evaluation of ECG interpretative programs.

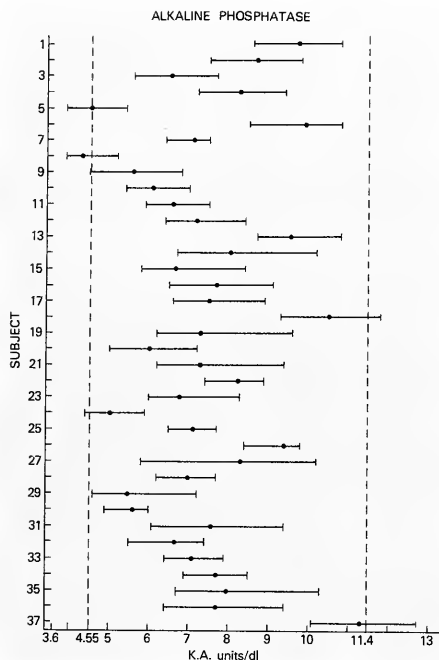
During FY81 LAS staff members participated in various teaching and consulting, or advisory, activities.

J. Fletcher continues to serve as Chairman of the Mathematics and Computer Science Departments, Foundation for Advanced Education in the Sciences.

J. Bailey continues as a member of an NHLBI site-visiting team concerned with computer analysis of exercise ECG's. He also serves as consultant on common standards for quantitative electrocardiography for an EEC-sponsored program in medicine and public health.

E. Harris continues to be a consultant in applied statistics to the Food and Drug Administration's Division of Medical Devices and Diagnostic Products. Dr. Harris also serves as consultant statistician to the College of American Pathologists and to the International Federation of Clinical Chemistry (Expert Panel on the Theory of Reference Values), and is a member of the Board of Editors of *Clinical Chemistry*.

During this reporting year, Dr. Adelin Albert, a mathematical statistician from the University of Liege, Belgium, joined the laboratory as a Fogarty International Research Fellow under Dr. Harris'



Charts like this one, which illustrates blood chemistry differences in healthy individuals, aid Dr. Harris in his collaborative studies.

preceptorship. Dr. Albert is developing and testing appropriate statistical techniques to utilize multivariate, serial data for optimal prediction of patient outcomes.

Highlights of Year's Activities

This year has seen substantial progress in all active LAS collaborative research projects, based in many cases on the technical advances reported last year in developing and implementing various computer systems. Some major accomplishments this year include:

- A joint project with the Pulmonary Branch and the Clinical Hematology Branch, NHLBI on the computerized analysis of pulmonary gas

exchange in normal volunteers and selected patient groups has been accelerated through the efforts of R. Burgess and E. Pottala of the Applied Mathematics and Medical Applications Sections. Complete redesign of analog circuitry has produced a reliable gas analysis system. The computer and computer-controlled exercise testing equipment has been specified, ordered, and, in large part, received. Dr. Burgess has also substantially increased the precision and sample size of the renal scintigraphy study on dogs, initiated during the prior reporting year.

- A major advance in the mathematical analysis of blood and substrate supply to tissue has been initiated by J. Fletcher (Chief, AMS). Incorrect solutions found in the existing literature for mathematical models of perfused tissue experiments have been corrected. The correct solutions to these and more general models are now being explored and will be used to predict distributed substrate levels for comparison with experimentally obtained microelectrode measurements.
- A comparative study of two ECG computer programs, based on ECG-independent clinical documentation of the presence or absence of various forms of heart disease in 284 patients has been completed and published by J. Bailey (Chief, MAS), M. Horton (MAS), and cardiologists at the Royal Infirmary in Glasgow. This study should provide a model for future evaluations of widely-used ECG programs because of the careful clinical documentation and the methods used to categorize ECG diagnostic output statements, allowing recognition of semantic equivalents despite differences in the terms used in different programs. The LAS investigators have extended their studies to the evaluation of serial computer-based ECG interpretations in a joint project initiated this year with Dr. D. Savage of the Framingham Heart Study, NHLBI.
- The PICTUR image processing computer package, developed and implemented last reporting year by M. Douglas (MAS) has been extensively applied, in collaboration with Dr. J. Costa (NIMH), to determination of the spatial distribution of fluorine within the dense bodies of

blood platelets. If continuing work proves successful, this fluorine-dense body system could become a reliable model for intracellular monitoring of therapeutic drugs in patients.

- M. Douglas and M. Horton (MAS) shared a DHHS special service award for their work with N. Crawford and V. A. Parsegian (Physical Sciences Laboratory) on computerized typesetting of scientific papers.

Future Plans

Installation of the computer-based gas analysis/exercise system will be completed and testing of normal volunteers will begin in cooperation with the pulmonary and clinical hematology branches of NHLBI. The scintigraphic studies of renal hypertension in dogs will be completed and the results will be prepared for publication. Expected progress in other active projects will include:

- application of generalized mathematical models to experimental data on organ perfusion with the goal of identifying the ranges of critical parameters controlling organ response to physiologic challenge,
- expanded collaboration with NIH laboratory scientists on application of network simulation programs to improving the understanding of molecular transport across membranes,
- development of appropriate physical and statistical theory to support the continued study of intracellular distributions of physiologically important molecules through electron beam analysis, and
- completion of comparative statistical analysis of multivariate and univariate time series applied to clinical laboratory data, using both real and simulated results of patient monitoring.

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Nancy Crawford shared an award with LAS members for her work with Dr. Adrian Parsegian on the computerized typesetting of scientific papers.

PSL carries out research to understand biological phenomena in terms of physics and chemistry.



Physical Sciences Laboratory

George H. Weiss, Chief

Function

The Physical Sciences Laboratory has three principal functions:

- *to carry out research* in the physical sciences in order to understand biological phenomena in terms of physics and chemistry
- *to develop theory and practical instrumentation* for biomedical experiments, and in particular to relate these to the capabilities of modern computer technology
- *to provide consulting services* to other scientists at NIH in physics, theoretical chemistry, and several fields in applied mathematics.

The staff of the Physical Sciences Laboratory consists of seven professionals who work in the areas of general biophysics, nuclear magnetic resonance, applications of light scattering techniques in biomedical experiments, the physical chemistry of polyelectrolytes, and problems in applied mathematics.

Scope of Work

The Physical Sciences Laboratory has a combined program of research projects internal to the laboratory and collaborative projects with scientists at NIH and at other institutions. The collaborative projects, done jointly with approximately twenty-five other investigators, include two major projects with data being generated by off-campus scientists.

Highlights of the Year's Activities

Although a large amount of time was devoted to getting bugs out of the 360 MHz spectrometer, useful experimental information is now becoming available. The advantages of being able to do pulsed and two-dimensional Fourier transform spectrometry are being exploited by Dr. James Ferretti in several ongoing investigations. He is investigating cross relaxation pathways in rigid organic molecules. Dr. Ferretti is also developing both theoretical and experimental aspects of Fourier transform spectroscopy allowing the deduction of internuclear distances and rotational correlation times by the use of cross relaxation. He has also concluded an investigation of the relation between errors in chemical shifts due to random and digitization errors. Specifically Dr. Ferretti has contrasted several

strategies for filtering and smoothing resulting data, finding optimal strategies for many cases of practical interest.

Dr. Adrian Parsegian and his collaborators have made several significant advances in the understanding of intermolecular forces in proteins and nucleic acids. Methods similar to those developed earlier by Dr. Parsegian to measure membrane-membrane forces are now being applied to the study of the aggregation, gelation, and crystallization of proteins, and to the packing of parallel double helical strands of DNA. This project will continue with the development of theory and experiments to systematically collect thermodynamic data on gelation and crystallization.

Dr. Ralph Nossal and his collaborators have performed experiments on experimental analogues of the flow of blood cells confirming an earlier theoretical development that allows one to interpret light scattering experiments *in vivo*. The combination of theory and experimental verification sets the stage for clinical applications of light scattering and in particular for the measurement of blood flow in capillaries, which has heretofore been impossible.

A theory has been developed by Dr. Nahum Gershon of the PSL and Dr. B. Aizenbud of MIT for diffusion on curved surfaces, with particular reference to fluorescent photobleaching recovery experiments. The major result of this investigation is that curvature does not affect estimated diffusion constants to any significant degree.

Dr. Parsegian was appointed Editor of the *Discussions of the Biophysical Society* and Dr. Weiss was appointed Mathematics Editor of the *Journal of the Washington Academy of Sciences*.



PSL develops theory and practical instrumentation for biomedical experiments.

Future Plans

With few exceptions, plans for the future involve building on scientific insights that have been gained in the course of PSL current research. Now that most of the bugs have been eliminated from the 360 MHz spectrometer, the next hope is both to develop methodology for two dimensional Fourier transform spectroscopy and to apply this technique to specific structure and configuration problems for biologically interesting molecules.

Studies of forces in membranes will continue with further analyses of the properties of sickle cell hemoglobin. Another project coming to fruition in the coming year will be a study of protein and nucleic acid contact using the molecular graphics crystal structures. These will enable investigators to vary configuration parameters to elucidate the contacts stabilizing protein dimers and tetramers.

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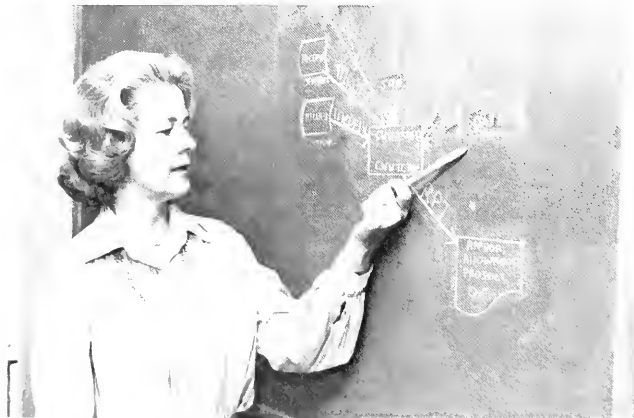
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Data base management technology provides both online and batch processing to meet various operational accounting and management control needs of NIH.

The Branch creates and maintains user-oriented tools, like RMAG, to speed building of programs and to improve operation of applications systems.

DMB supports the NIH data base management system, which, when complete, will handle nearly all NIH materiel and financial transactions.



Data Management Branch

J. Emmett Ward, Chief

Functions

The Data Management Branch (DMB) provides advice and assistance to research investigators, program officials, and administrators throughout NIH in planning for and obtaining computer data processing services. In this role the branch is a central NIH resource for systems analysis, design, and programming. There are currently 47 permanent full time employees whose disciplines include computer science, mathematics, and statistics.

Scope of Work

DMB staff design and create computer-based data management systems that provide practical solutions to the unique mix of administrative, scientific and management data processing problems encountered at the NIH. Each new computer system user is provided comprehensive training in all system facilities and functions. In addition DMB staff teach courses about data management and DMB programming tools; they provide advice on data management techniques to NIH programmers; they serve as consultants to the B/I/D's for obtaining and monitoring contracting services for computer systems development; and they create and maintain general purpose, user-oriented programming tools to speed building and improve operation of applications systems.

The DMB comprises five sections. The **Applied Systems Programming Section (ASPS)** and the **Scientific Applications Section (SAS)** provide general computer systems analysis and programming services for all of the B/I/D's. The ASPS supports general data management, and the SAS handles those projects which require scientific data analysis.

The **Data Base Applications Section** and the **Data Base Enhancement and Control Section** develop and maintain the central administrative data base for NIH materiel and financial management. The **Clinical Support Section** develops and maintains the Clinical Information Utility as a data base for research and patient care in the Clinical Center.

FY81 Accomplishments

In the NIH Administrative Data Base system, during the first quarter, the demands for ad-hoc reporting and the significant increase in maintenance of the backup and general reporting functions for data base management required another shift of Branch personnel. The Software Support Section was abolished and its primary function was transferred to the Office of the Chief. Two people were transferred to the Data Base Applications Section to assume the maintenance and reporting functions.

As a result of this transfer, major progress is being made to streamline the backup and maintenance functions and to standardize software for both ad-hoc and recurring reports. A commitment source data system, which:

1. controls telephone charge agreements, basic purchase agreements, and indefinite delivery contracts
2. monitors records of call and telephone charge orders against these agreements and contracts
3. validates and summarizes fund and accounting information
4. enables automatic generation of vendor identification and address on purchase documents,

has also been installed on the administrative data base. This provides managers, purchasing personnel, and financial clerks with fully synchronized information on the status of all source commitment documents.

A delegated procurement and receiving entry system was completed during the year and is now in the process of being installed on site in the B/I/D's. When it is completely installed, the movement of all paper actions relating to delegated purchasing and receiving will end, and the computer data base will be the source for all information except the locally signed, legally required hard copy documents.

In the accounts payable area, DMB has provided a full invoice inventory procedure which ties the invoice process to the purchase order. When orders are eligible to be paid, invoices are automatically displayed to the voucher examiner, preliminary payment schedules are electronically prepared and presented for review, and final schedules to Treasury are released through the computer system. The experience gained in working with staff of the Division of Financial Management (DFM) has also

led to the streamlining of manual and machine procedures which optimize the entire payment process.

In the NIH Clinical Information Utility (CIU), development this year has concentrated on implementing the weekly cumulative laboratory summary and on reducing the size of the hard copy medical record. It became clear that producing complete retrospective summaries each week not only required an unacceptable level of elapsed computer time to produce, but also literally inundated the medical records staff with weekly volumes of old and new paper. To eliminate both problems, it was agreed that only permanent medical record replacements would be provided every six months. A sophisticated computer system was developed to provide this capability. This new system balances the volume of the permanent replacement paper flow and collates the permanent and weekly summaries in a way that assures ease of handling by medical records personnel.

Further reduction of the medical record is now in the requirements analysis stage. Specific consideration is being given to: identification of information required legally and medically in the record, requirements for access and display of high and low use medical records data, and methods and modes of electronic, hard copy, and other alternative forms of storing medical records data. The final design of either a system or systems to accomplish a reduction in the bulk and optimization of access and display of medical records data is hoped to be completed by January 1982.

Another clinically-oriented project, which eventually will require an interface with the CIU, is the extension and enhancement of the BRIGHT system to provide Clinical Center investigators the ability to perform online analysis of their own clinical data. A t-test module and a plotting module have been added recently to BRIGHT. Other modules--to provide descriptive statistics, chi-square test, linear regression, ANOVA, normality test, non-parametric tests, and life table analysis--are planned. Modules will be added as new requests are received from investigators.

In addition to this work on central NIH administrative and medical data management facilities, the

significance and breadth of DMB's involvement in the NIH mission is evident in many computer systems it has developed to support individual scientific, administrative, and management projects during the past year. Virtually every B/I/D has benefitted from services provided by the DMB. Each of these systems has served a vital segment of NIH and, when viewed together, they illustrate DMB's very reason for existence as a central resource for all of NIH.

In the area of general support for NIH activities, DMB continued to maintain and teach courses on the Inquiry and Reporting System (IRS) and MARK IV; to support NIH use of Chemical Biological Activities (CBAC) and Biosciences Information System (BIOSIS) awareness searches on a biweekly and semimonthly basis, respectively; to maintain and distribute the NCI Survival System; and to consult with and assist NIH programmers and contractors, enabling facile use of DCRT computer facilities.

The Scientific Applications Section (SAS) is developing a computer system that will enable Clinical Center investigators to analyze their own data.



Future Plans

The Clinical Support Section will begin, by January 1982, software development for the system or systems to reduce the size and optimize the use of medical records data. As a by-product of this effort, it is anticipated also that requirements for an integrated CIU data base will be defined and the software development for this effort can begin shortly afterwards. As each new benefit becomes available, it will be phased into the day-to-day functions of the Clinical Center.

New functions anticipated to be added to the NIH Administrative Data Base system include: stock requisitioning, central and self-service stores inventory, open market requisitioning, accounts receivable, and vendor credits. The requirements study for an upgraded financial management system should be completed by the end of this calendar year; a system should begin shortly after that.

In addition DMB will continue its primary role as a central resource for computer applications development to all components of NIH that need this service.

Publications

- Harris, E.K., Yasaka, T., Horton, M.R., and Shakarji, G.: Comparing Multivariate and Univariate Subject-specific Reference Regions for Blood Constituents in Healthy Persons (in press).
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Bill Jones, Carol Kahl, Jennifer Fajman, and Roger Fajman were some of the computer professionals involved in designing the new version of WYLBUR.

The NIH Computer Utility provides services to over 8,000 users and processes about 21,000 job sessions each day.



Computer Center Branch

Joseph D. Naughton, Chief

Function

The Computer Center Branch (CCB), the largest component of DCRT, designs and operates the NIH Central Computer Utility and its associated online telecommunications facilities, in support of scientific and administrative programs throughout NIH.

Two large multi-computer facilities, the IBM System 370 and the DECsystem-10, form the nucleus of the Computer Utility. These are linked by communications facilities and connected by telephone lines to hundreds of remote interactive terminals located in research laboratories and administrative offices throughout NIH. Complementing this array of systems hardware is a complex set of software, either designed and implemented by Center personnel or acquired from other sources and adapted to meet the unique requirements of the NIH biomedical research program.

Approximately 140 professional, technical, and administrative personnel ensure the smooth functioning of the NIH Computer Utility 24 hours a day. The computer specialists, programmers, and systems analysts design, implement and maintain the complex computer systems software that monitors and controls the flow of work through the system. They also design and conduct extensive training courses, write and publish technical documentation on the use of the Utility, assist users in problem diagnosis, and maintain and schedule recurring production applications. Experienced technicians operate the computer systems and auxiliary equipment and provide data entry services. The remainder of the staff provides the necessary administrative support for this complex work.

Research and development projects are active in the areas of scientific image processing, computer networking and communications, text editing, display of biomedical objects, and utilization of mass storage devices.

To augment the function of the Central Computer Utility, the Computer Center provides systems programming support, consultation, documentation, and training.

Scope of Work

The NIH Computer Utility provides services to over 8,000 authorized users. These include research scientists and program managers from every area of NIH. The IBM System 370 facility is used as a Federal Data Processing Center for biomedical and statistical computation by authorized staff in 24 other Federal agencies. All services are provided on a cost-recovery, fee-for-service basis through the NIH Service and Supply Fund.

A variety of programming languages--including FORTRAN, COBOL, PASCAL, BASIC, SPEAKEASY, PL/I, and SAIL--are available, as well as a data base/data management system (IMS) and a comprehensive library of utility programs. Direct interactive computing and batch job services are available through WYLBUR, TSO, and through similar interactive systems on the DECsystem-10. The Center provides several facilities for job output on paper and microfiche and has programs for creating two- or three-dimensional graphic displays for advanced projects such as those involving macromolecular structures.

The work load of the Computer Utility has grown steadily since it opened in 1968, and FY81 has been no exception. The Computer Utility processed an average of 21,000 job-sessions per day during the past year. Workload on the IBM System 370 exceeded half a million job-sessions per month for the first time in October 1980 and in March 1981 reached 544,248. The DECsystem-10 timesharing facility, utilizing new equipment acquired late last year, continued to expand its services and workload.

Highlights of the Year's Accomplishments

The past year has been an especially important one, with major achievements being made in a number of areas.

--The long-awaited new and greatly enhanced NIH version of WYLBUR became operational on January 8, 1981 for all users of the Utility. An 11-week transition period, during which both old and new versions were available, proved to be exceptionally smooth; user reaction to the new features of this interactive, terminal-oriented facility was enthusiastic. The improved document formatting and new command procedures facilities proved to be especially popular. The document formatting capability facilitates the production of all types of documents. Command procedures can prompt for and validate data and can automate repetitive work within WYLBUR, providing improved productivity in many types of computing applications.

--One of the largest procurements ever conducted by NIH was brought to a close this year as a ten-year, 'total system' contract was formally signed with IBM Corporation. IBM agreed to provide hardware, software, maintenance, and support services to the NIH Computer Center throughout the 1980's, enabling the Center to meet NIH's information processing needs efficiently without the lengthy procurement delays that occurred frequently in the past. The contract allows rapid utilization of new technologies as they are developed by industry and provides the flexibility to adapt to changes in workload, thus permitting improved cost effectiveness.

--Advances were made in the renovation of Buildings 12 and 12A. The plotter and the bursting equipment were moved closer to the computer room on the first floor of Building 12A, resulting in improved turnaround for these services. Construction of modern classrooms and a new graphics systems area began in the basement of Building 12A. A new, enlarged user terminal area and the new classroom facilities are expected to be completed in early 1982.

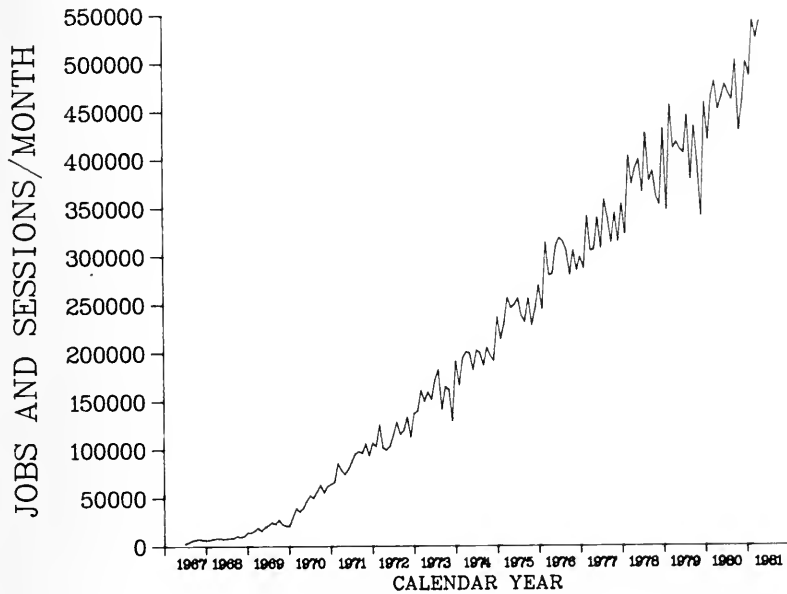
--Major work was accomplished with the molecular graphics system this year. Activities included determination of structures by crystallographic methods, display of known structures, and modeling of hypothetical structures. The coordinates for two virus structures were determined during the year.

Techniques for extending known protein structures to other members of the same family were also developed. This enabled modeling of hypothetical structures of immunoglobulins, myoglobins, and the clotting factor proteins. The most exciting experiment involved trying to predict the correct architecture for proteins where only the primary structure is known. The first result at this level is a model for the structure of the human leucocyte interferon.

--In FY81 as in previous years, the Computer Center evaluated available hardware and software components. It selected and installed those that serve best to help the Center meet computing needs of NIH. This year additions include:

- A PASCAL/VS compiler for the IBM 370 to make PASCAL, a language used widely by computer scientists, available on both systems of the Computer Utility
- SPEAKEASY, a language designed at the Argonne National Laboratory for scientific and mathematical problem solving
- DISSPLA and TELL-A-GRAF, commercial systems that provide extensive facilities for creating graphic output and make these facilities available to users having graphic display terminals.

*NIH COMPUTER UTILITY
SYSTEM 370 SERVICES*



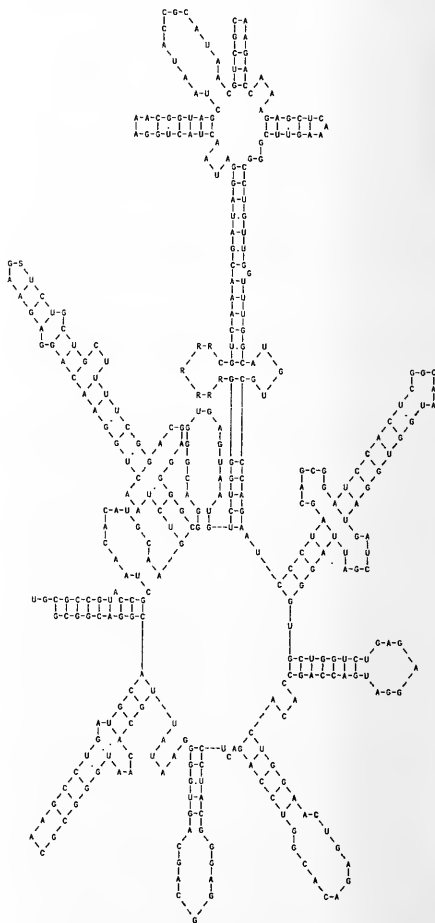
Future Plans

Completing the installation and integration of the new IBM equipment and developing the full operating capacity of both the DECSYSTEM-10 and the IBM System 370 will remain important goals of the coming years. Installation of new IBM equipment will continue into the coming year as old equipment is gradually phased out and replaced with newer, faster, and more reliable technology. For instance, the 3380 disk drive, IBM's newest disk drive, will be installed toward the end of 1981. The new disk drive, which will provide both local disk workspace and shared permanent storage, will triple the storage capacity of the system and provide greatly enhanced operating speeds as well as increased reliability.

Improving the reliability, availability, and performance of the Computer Utility is a continuing goal of the Center. However, the Computer Center faces a major challenge as it endeavors to continue improving services while responding to the current need to reduce operating expenses and limit staff size. To meet this challenge, the Computer Center has established a special support level for non-critical software. While essential software will continue to receive full support service, less widely-used products will be designated to receive limited support. This lower level of support will exclude consulting and assistance with problem diagnosis and will provide only limited maintenance service. The new policy will allow the Computer Center to continue expanding software offerings without jeopardizing quality of service and responsiveness.

The coming year will also see completion of the building program, installation of security facilities to improve data security, and development of simpler capabilities for output processing on the JES2 facilities. Several new training courses will help users take maximum advantage of new features of WYLBUR; these include an introductory WYLBUR course for programmers, courses on document formatting and command procedures, and a series of seminars on advanced topics in WYLBUR.

Nucleic acid type picture for a fragment of E. coli 16S RNA.
 *** R. Brinacombe, *Biochemistry International*, 1(2) pp. 162-171, 1980.



Two-dimensional computer graphics like this one, which shows the nucleic acid sequence for an RNA fragment, help scientists in their investigative work throughout NIH.

Publications

Feldmann, R. J., and Bing, D. H.: *Teaching Aids for Macromolecular Structure*. New York, The Taylor-Merchant Corp., 1980, 98 pp.

The three DCRT Offices complement the work of the six Laboratories and Branches by:

- coordinating the complex Federal policies and procedures that govern getting and using computers at NIH
- providing general administrative management support for the Division's work
- serving as a central source of information about DCRT activities and about computer-related disciplines.



The DCRT Library maintains a collection of about 6,000 books and technical reports on computer science, mathematics, statistics, engineering, management, and information science.

Gloria Crawford, the DCRT Administrative Officer, supervises all travel, training, forms management, Privacy Act, and business functions of the Division.



Mike Reed and Julia Neel of the Financial Management Section oversee the financial operation of DCRT.

Office of ADP Policy Coordination

Henry J. Juenemann, Chief

Functions

The Office of ADP Policy Coordination, under the direction of the Assistant Director of the Division, has three closely related functions:

1. It is a focus for NIH-wide coordination of automatic data processing (ADP) policy matters.
2. It serves as a central NIH point of contact on policy and regulatory questions with the Public Health Service, the Department of Health and Human Services, other HHS Agencies, and the General Service Administration.
3. It provides advice and assistance concerning the internal operations of DCRT in matters of ADP policies and regarding interagency sharing agreements with other Federal agencies.

Scope

The role of the office includes:

- advising the Director of DCRT and through him the Director of NIH on ADP policy matters
- reviewing and evaluating proposals from NIH B/I/D's for procurements and contracts related to computing and ADP
- directing the development of the annual NIH ADP Plan
- assisting the NIH Division of Management Policy on questions relating to its responsibility for administrative and management computer applications
- representing NIH in PHS and DHHS policy formulation efforts
- working with GSA staff to obtain necessary approvals for NIH on procurements and contracts
- coordinating interagency agreements with other Federal agencies that use DCRT facilities, and
- answering inquiries from scientists and administrators who are confused by the whole process.

This office has grown over the years in the breadth of its activities but not in its size or cost. This fact is strikingly analogous to the growth of the ADP technology itself over the last decade and a half. The functions of the office have evolved to solve problems as new problems arose, to adapt to change as changes occurred and to fill gaps as they

became obvious. This is strikingly similar to the parallel changes in computer technology itself, where every year has been marked by increased capacity and capabilities applicable to a wider range of problem areas but still attainable with resource expenditures of similar or smaller magnitude as those of the older technologies being replaced.

Highlights of FY81 Activities

A major highlight of the year was completion of the complex reprocurments of both systems comprising the NIH central computing facility. After a protracted five year process and in spite of a GAO protest, award of a contract was made representing a full reprocurement of the general purpose IBM 370 system. The resulting contract provides NIH computer users with a long period of stability while also permitting flexibility to respond promptly to technological and workload changes. Likewise, reprocurement of the DECsystem-10 scientific time sharing system was completed to provide a combination of a period of stability with the same flexibility to adjust to change. Both reprocurements were accomplished in a way that had no adverse impact on their user communities.

During the year this office reviewed nearly 600 proposals for acquisition of ADP equipment and/or services. Each was reviewed to ensure that it was justified and was in conformance with PHS, HHS, GSA, and OMB guidelines. Suggestions and assistance were provided to the NIH Procurement Branch and to contracting officers in Research Contract Branches as to the most expeditious procurement route to follow. In many cases one or more of the Laboratories and Branches of DCRT assisted by providing expertise to help in the review of technical aspects of the proposals.

The office arranged the transfer of a computer system from DCRT to the National Library of Medicine, for relocation in a computer room in the Lister Hill Center building. This action resulted in a significant increase in NLM capacity to support its information retrieval activities and made possible savings estimated to be nine million dollars over the next three years.

Arrangements were also made for the system thus discontinued by NLM to become the primary support system for the NIH Clinical Center Medical Information System. It replaced a much older and more limited contractor-operated system for meeting day-to-day patient care information needs of the NIH Clinical Center. The transfer included arrangements for the Clinical Center to make use of the computer room facilities formerly used for the NLM system. The transfer satisfied for the first time the vital need for backup redundancy in a system which--24 hours a day, 7 days a week--serves all of the wards and clinical services in a patient care environment. This relocation resulted in an anticipated saving of 1.5 million dollars over a 28-month period.

During the year a number of cell sorter and image processing computer system procurements were expedited as well as procurements of a variety of other automated equipment including, this year, many microcomputers. An RFP was issued for the automation of the NIH Library; a contract award is expected in the last few months of the year so that implementation of the initial phases of the project can begin.

At year end the most time-consuming undertaking of this office was the effort to extend DCRT's program to supply users with several varieties of 'NIH Standard' terminals. Having standard terminals maximizes efficiency of the Center and of the users who access the NIH central computing facilities. Extension of contracts for the three existing types of standard terminals was being sought as was expansion of the program to cover those needed for the new NIH Administrative Data Base System.

The Annual ADP Plan--which combines projections of new ADP initiatives and required ADP expenditures for all bureaus, institutes, divisions, and offices of NIH--was completed. It details an NIH ADP program projected to be 62 million dollars and 783 work years in FY82 growing to 88 million dollars and 833 work years by FY87. Although the accuracy of the out-year projections must be regarded with caution, the trend of ADP and computing involvement in the scientific and managerial life of NIH is unmistakable.

Future Plans

FY82 will be marked by major changes in the structure, staffing, and focus of NIH's overall ADP Policy Coordination functions. These changes, the nature of which are not predictable at this writing, will be accomplished during FY82.

Office of Administrative Management

L. Lee Manuel, Chief

Function and Scope of Work

The Office of Administrative Management, under the direction of the Executive Officer, consists of 15 people, organized functionally into three sections: finance, personnel, and general administration. The office serves as liaison between these functions and the NIH Office of Administration, Office of Research Services and with other NIH, PHS, and DHHS offices. It handles a broad range of administrative managerial functions for an NIH research division of almost 300 people.

Fiscal Year 1981 Accomplishments

The Administrative Office processed a vast number of administrative actions and acquired approximately 30 million dollars in supplies and equipment during FY81. Day-to-day management activities conducted by this staff included: procurement purchases and contracts; travel; training; the administration of property, space, and communications; payroll; and mail/messenger services. As a result of new and pending delegations, the position descriptions of the staff were reviewed and restructured as necessary to better take advantage of these authorities. An automated system was developed to track and report travel plans and obligations.

During FY81 the Project Control Office conducted a major update of its files of information on 8,000 users under some 2,000 project accounts. The Project Control Officer also was appointed Assistant Systems Security Coordinator for the Division and was charged with operational responsibility for meeting departmental guidelines and reporting requirements relating to ADP systems security.

The Budget Office spent most of the year coping with a continually decreasing Management Fund budget and increasing reporting requirements to NIH program officials on various detailed levels, such as travel and consultant services. The office studied the impact of estimated 1981 operating expenses in the fee-for-service areas along with workload/income projections. Division cost center managers negotiated rates for various services with the Division of Financial Management.

DCRT acquired its own personnel staff as a result of the Division of Personnel Management decentralization. As a result a DCRT Personnel

Officer was appointed for the first time and several delegated authorities, such as position classification, were acquired. The Personnel Office provided DCRT with advice and assistance in several areas.

During FY81, approximately 400 personnel actions that included promotions, reassignments, temporary appointments, excepted appointments, and transfers were processed. In February 1981, hiring outside the Department was restricted to hardship appointments and clinical case positions only; DCRT was not affected. Recruitment efforts have been solely departmental for vacancies we have been able to fill. The hiring freeze and Reduction In Force within PHS increased the supply of applicants for the computer specializations, but have made it difficult to retain our computer operators, an area in which we have experienced a large number of losses.

DCRT is serving as the NIH-wide focal point in the development of Performance Elements and Standards for the Computer Specialist, Technician, Mathematics, and Statistics occupational groups. This effort is being carried out for implementation of the Performance Management System (PMS) to be instituted October 1981. The Personnel Officer also took the leadership role in implementing the Factor Evaluation System for the 334 (computer specialist) series and for the PMS.

Future Plans/Trends

Contracting, procurement, travel, and consultant service requirements as mandated by PHS and Office of the Secretary, DHHS involve intensive monthly and quarterly reporting of financial procurement plans vs. the actual commitment and numerous other reporting requirements for consultant services, travel, budget reductions in equipment, and other items. To meet this need, we plan to cross-train existing staff and to decentralize the entering of procurement actions into the NIH Materiel Management System.

The Financial Management/Project Control Section will develop budgets at the laboratory level within the Division and will implement a system reporting to the lab chiefs on expenditures. A revised Project Control Office form is being developed to ease the annual process of updating files.

Office of Scientific and Technical Communications

William C. Mohler, M.D., Chief

Functions

The DCRT Office of Scientific and Technical Communications (OSTC), under the direction of the Associate Director, DCRT, includes:

- The DCRT **Library**, which maintains a collection in computer science and mathematics, statistics, engineering, information science, and management
- The DCRT **Information Office**, which serves as the focus for providing the NIH community and the general public with information about DCRT's activities and their relationship to biomedical research
- **Scientists** assigned to this office, working in related areas of pattern recognition, multidimensional information processing, and applications to medical decision making.

Scope of Activities

The DCRT Library is a small, independent, special library, staffed by the Librarian and a library technician. The staff members provide a full range of library activities and have access to a wide variety of online information services and data bases. The collection of monographs, periodicals, and other documents covers subjects related to the work of DCRT. These include computer science, mathematics, statistics, electronic engineering, information science, and management.

The Library supports the work of the DCRT staff and serves as a resource for employees in the rest of NIH. It is an integral part of the Washington area network of special libraries and cooperates with libraries outside the area to share resources. It does this through organizations such as the Interlibrary Users Association of the Washington/Baltimore Area, the Metropolitan Washington Library Council, FEDLINK (a Federal library consortium), and--at the national level--the OCLC (Online Computer Library Center) network.

The DCRT Information Office, too, is small and handles the full range of activities of an NIH Information Office. The Information Officer, assisted by a Public Information Specialist, answers inquiries, produces and distributes print and audiovisual materials, and arranges briefings for visitors. They coordinate special events, work with members of the

media and provide advice, assistance, and educational resources on communications for the DCRT staff. The office is responsible for all Freedom of Information requests coming to DCRT.

A significant part of the Information Office program is directed toward improving within NIH an understanding of the Division's work and the application of computing to biomedical research. But the scope of its communications includes Federal agencies, schools, libraries, private industry, medical organizations, and a wide variety of individual scientists and lay persons. The Information Officer is active in the NIH information community and in Washington area associations of communication professionals.

The other professional activities of OSTC derive from the interests of its scientific professionals. They work with other professionals at NIH and with medical and technical groups, government and private, outside of NIH. They have research and development projects on image processing and decision analysis.

Highlights of FY81

The DCRT Library maintained its excellent services to users during FY81 in spite of transient vacancy in its library technician position and a period of extended sick leave for the Librarian. Indeed the number of books circulated and online bibliographic searches made surpassed those of the previous year. The new Library Technician, Anita Fiorentino, came to DCRT with six years experience from the Technical Services Branch of the NIH Library. She and the Librarian, Mrs. Chu, cleaned up the accumulated backlog in processing library materials by closing the Library to users one afternoon a week during the early spring. Preliminary design and drafting is complete on a new Library user's brochure to replace the old (1971) version.

The computer-based Circulation System and Document Indexing Systems installed in previous years by the Library with the help of DCRT staff continued to function well and to assure timely availability of books and documents to DCRT staff and to other Library users. The Librarian was a guest speaker on the realities of library automation at a meeting of the Special Libraries Association in

Washington, D.C., and served with other DCRT staff on the Advisory Task Force on Automation for the NIH Library. She completed her year as Chairperson of the delegation from FEDLINK (the Federal Library Network) to the Users Council of (OCLC Online Computer Library Center), a national cooperative library network. She was elected a Director and member of the Executive Board of the District of Columbia Library Association.

With the assistance of the DCRT Library Advisory Committee, the Librarian completed a review of journal holdings, made major revisions to the list of journals for subscription in FY82, and set new criteria for holdings of back year copies as hard copy or microform. The Librarian participated with other DCRT and NIH staff at meetings to advise on collection policies for books in mathematics, statistics, engineering, and physics at the NIH Library. The consensus held that the NIH Library should have an up-to-date, if limited, set of books in these areas for all NIH. The DCRT Library assumed responsibility for the collection of highly theoretical and advanced works.

The DCRT Information Office had a busy and productive year.

The office produced a 22-minute videotape program documenting two DCRT projects dealing with computer voice technology. The first of these two systems dealt with a computer voice output system developed by CSL and now in use by a blind computer programmer. The tape also dealt with an existing computer voice input system being used by a quadriplegic programmer employed by DMB. During the International Year of Disabled Persons (1981), the videotape was distributed nationwide to 100 organizations serving the handicapped, to several other Federal agencies, and to a local media outlet. The tape was made available to approximately 180 public television stations throughout the United States and its territories. PBS member station WETA-TV in Washington, D.C. aired the program in March, 1981.

A short sound/slide show describing DCRT and the work of its laboratories and branches was also created.

The Information Office prepared new brochures for

LSM, DMB, and the DCRT Library, and assisted in the production of the CSL brochure. The office reprinted *Computers at NIH: Tools for the Advancement of Medicine* and issued an update of *Computing Resources*, the compendium of who does what in DCRT, designed to help NIH staff understand how DCRT can aid NIH scientists and administrators.

Coordinating and producing the FY81 DCRT Annual Report was another major job. The FY80 version received an Award of Achievement from the Society for Technical Communication, Washington Chapter.

A third communications course, 'Effective Listening,' was organized. Thirty-five Division staff members received this training. This course complements the 'Effective Speaking' and 'Effective Writing' courses given in previous years.

Both public inquiries and publication distribution remained at levels similar to those of last year. The Information Office handled approximately 30 special inquiries and distributed about 300 publications each month. The general public and other B/I/D's made up the majority of the DCRT audience, but a significant number of students and schools also received materials. Several groups received a DCRT briefing and tour, including scientists from China and Japan. Information Office staff members also visited several nearby colleges to discuss DCRT's role at NIH and the application of computers to biomedical research.

The Information Officer continued independent research work on preparing text in magnetic format for direct typesetting by GPO; this may result in a system ready for NIH-wide use by the end of the calendar year. She was appointed Chair of the NIH Printing Committee. In addition, she was also active in outside professional organizations, heading a panel on evolving technologies in editing for the annual conference of the National Association of Government Communicators. She also served as president of the 350-member Washington chapter of Women in Communications, Inc., a national organization for public relations, journalism, broadcasting, and communications professionals.

Work of the scientists assigned to the office continued along lines it has followed in previous

years. The areas covered are best seen in the list of publications and presentations. Dr. Judith M. S. Prewitt, research mathematician in the Office of the Director, was elected Fellow of the Institute of Electrical and Electronics Engineers (IEEE). She is also an officer of several scientific societies and an editorial board member of four scholarly journals: *IEEE Transactions on Pattern Analysis and Machine Intelligence*, *Computer Graphics and Image Processing*, *Medical Decision Making*, and *Analytical and Quantitative Cytology*. She is a National Visiting Lecturer of the Society for Industrial and Applied Mathematics as well as its representative to the American Association for the Advancement of Science, Mathematics and Statistics Sections. She has just been appointed first Chairman of the new IEEE Computer Society Technical Committee on Computational Medicine.

Plans

The Library and the Information Office will support the needs of DCRT and NIH within the limits set by available staff and funds. The Library will continue to work on changing catalog records to conform to the new forms of the revised Anglo-American Cataloging Rules (AA CR 2). It will explore the applicability of computer systems to support this task and to keep up with the effects of automation by the Library of Congress on its catalog. As a first step, the Librarian and DCRT volunteers reviewed older monographs to weed the collection. The retrospective conversion on the OCLC system will begin during the summer of 1981. Catalog records for items added to the library prior to 1976 will be tagged for inclusion on the DCRT holdings tape. The DCRT Library will use computer programs written by the Computer Systems Laboratory for preliminary processing of the OCLC tapes.

The Information Office will continue to develop and improve materials to tell people what DCRT does and how computers are used in biomedical research. This may include some new materials for use at NIH and perhaps for export in response to requests from outside NIH. The Information Office will survey both DCRT and NIH to bring up to date the list of needs for communications about computers at NIH.

Publications and Presentations

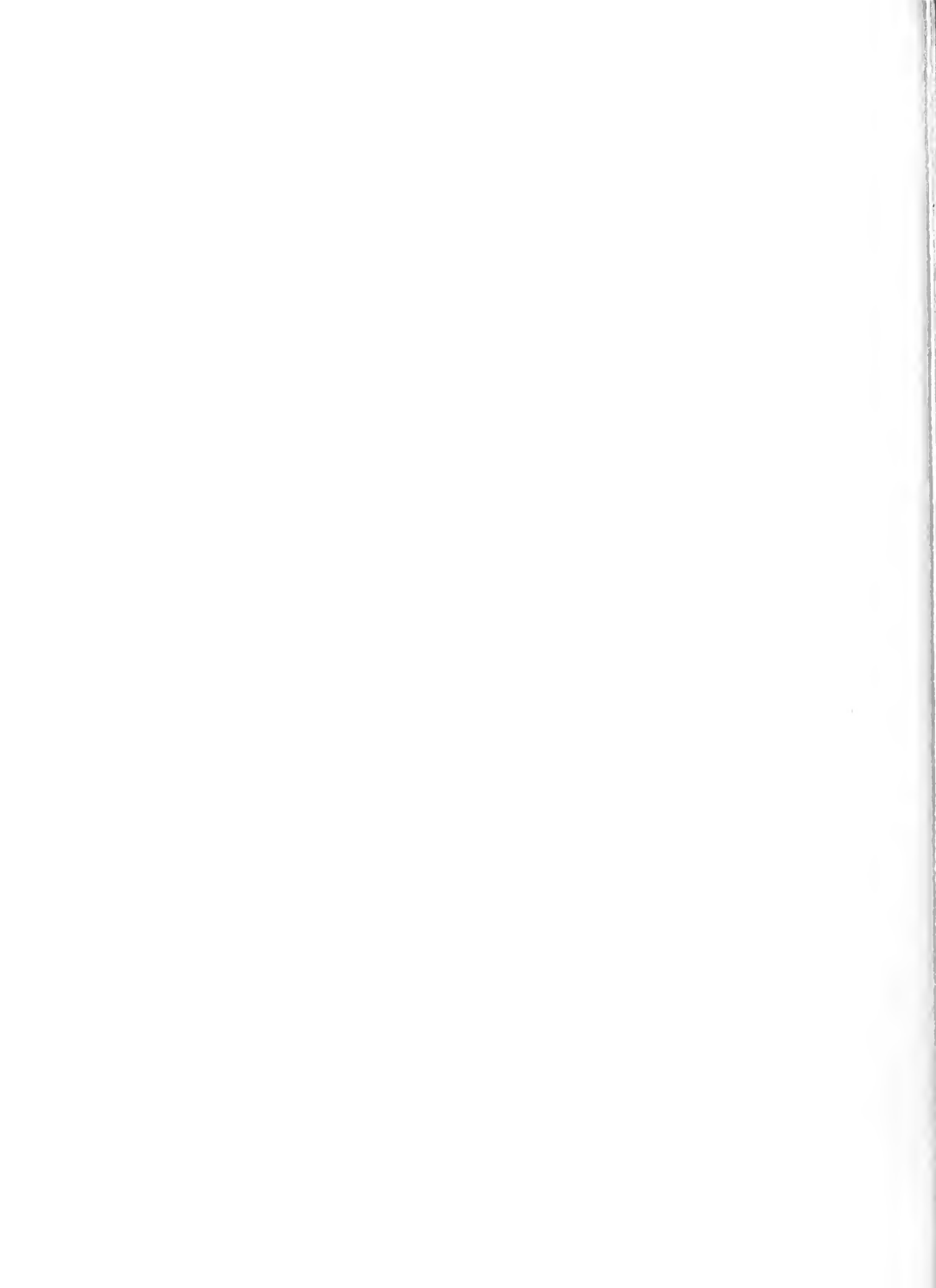
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Division of Computer Research and Technology
National Institutes of Health
Bethesda, Maryland 20205

VOLUME 2



DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

FISCAL
YEAR
1981

ANNUAL
REPORT

VOLUME 2



Foreword

The work of the Division of Computer Research and Technology covers a large spectrum of activities. It ranges from doing research in biology, statistics, mathematics, and computer science to providing computer facilities and services for NIH.

The several DCRT laboratories and branches embody and integrate this variety of talents. Each has a major functional focus. But the success of the Division's work arises from the interaction of members of each group with others across organizational and disciplinary lines. Many projects in the Division require the expertise of people from several segments of the spectrum.

DCRT's collaborative projects link its staff to professionals both inside and outside NIH. The result is a balance in emphasis to provide the work done by DCRT at NIH with the benefits of collaborations outside of NIH.

While DCRT does not have money for grants, it does provide occasional support for meetings on scientific topics related to its work.

This year's annual report is presented in two volumes:

- **Volume 1** gives a summary overview of the work of each group and highlights its accomplishments.
- **Volume 2** includes detailed projects and activities of each group.

If you have comments on the report or suggestions for improving future annual reports, please send them to:

DCRT Information Office

Building 12A, Room 3027

Division of Computer Research
and Technology

National Institutes of Health
Bethesda, Maryland 20205

Contents

Laboratory of Statistical and Mathematical Methodology

Summary of Activities 7

- Computation 7
- Consultation 8

Research Projects 10

- Automated Data Processing of Medical Language 10
- Cluster Analysis 11
- Research Topics in Computer Science 12
- Discrete Mathematics and Applications 13
- Biological and Visual Shape 14
- Multivariate Statistical Analysis 14
- Linear Methods in Statistics 15
- Non-numerical Programming Techniques and Applications 16
- Topics in Geometry and Analysis 17

Computer Systems Laboratory

Summary of Activities 19

Research Projects 24

- Computer Support for Flow Microfluorimetry/Cell Sorters (FMF) 24
- Distributed Laboratory Data Acquisition and Control System 25
- Molecular Interactions Laboratory Data System 27
- Californium-252 Plasma Desorption Mass Spectrometer Data System 27
- Combined EDS-WDS X-ray Analysis Scanning Electron Microscope System 28
- Cardiac Scintillation Probe 28
- Medical Intensive Care Unit Patient Monitoring Computer System 29
- Cardiac Intensive Care Unit Patient Monitoring Computer System 31
- Computerized Radiation Therapy 32
- Image Processing Facility 33
- Digital Imaging Applications in Cardiovascular Research 34
- Cerebral Metabolic Imaging 35
- Computer Analysis of Gel Electrophoresis 36
- Automated Analysis of Plaque Formation in Experimental Atherosclerosis 37
- Computerized Three-Dimensional Model of the Cat's Brain Stem 38
- Rehabilitation Medicine Department Computer System 39
- Image Processing of Electron Micrographs 40
- Positron Emission Tomography (PET) Scan Image Analysis in Aging Studies 41
- Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies 42
- Cataract Grading via Computerized Slit-lamp Image Analysis 43

Image Analysis in Computerized Tomography (CT)

- Contrast Material Evaluation 44
- Image Analysis in Automated Radiotherapy Treatment Planning 45
- Automated Pulmonary Physiology Testing 45
- Measurement of Transepithelial Resistance of Kidney Tubule 47
- Electron Microanalysis Facility 48
- Computer Assistance for Blind Computer Users 49
- Metabolic Energy Measurements 50
- Medical Information Technology Project 51

Laboratory of Applied Studies

Summary of Activities 53

Research Projects 55

- Statistical Research in Clinical Pathology 55
- Mathematical Models of Binding Equilibria 57
- Mathematical Modeling of Substrate Transport in Physiological Environments 57
- Analysis of Coupled Transport and Biochemical Kinetics 59
- Nonlinear Equations 62
- Numerical Approximation Techniques for the Solution of Reaction-Diffusion Systems in Biology 63
- Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease 65
- Investigation of Hybrid Computing for the Construction of Simulation Models and for the Analysis of Physiologic Signals 66
- Computer Systems for Nuclear Medicine 67
- Computer-Aided Analysis of Electrocardiograms 69
- Computer-based studies in Ultrasonography 70
- Computer Based Analysis and Image Processing in Electron Microscopy and X-ray and Electron-Loss Spectroscopy 71

Physical Sciences Laboratory

Summary of Activities 75

Research Projects 77

Consulting Services 77

Theory of Biochemical Separation Techniques 77

Actin in Nonmuscle Cells—Biophysical and Biochemical
Studies 78

Theory and Application of Nuclear Magnetic Resonance
Spectroscopy 79

Correlation Function Spectroscopy/Laser Light Scattering 81

Cell Motility and Chemotaxis 81

Theory and Measurement of Intermolecular Forces 82

Studies in Mathematics and Statistics 83

Quantitative Analysis of the Electronmicroscopy of Cells
and their Plasma Membrane 84

Diffusion of Molecules on Cell Surfaces and Light
Scattering from Fluids 85

Computerized Typesetting of Scientific Papers 87

Data Management Branch

Summary of Activities 89

Computer Center Branch

Summary of Activities 95

Research Projects 97

Nucleic Acid Structure Synthesis and Display 97

Office of the Director

Summary of Activities 98

Research Projects 99

Text-to-tape Copy Preparation 99

Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

Summary of Activities

LSM activities can be divided into three areas: computation, consultation, and research.

Computation

A major part of LSM activity is the offering of statistical and mathematical systems/packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does support a system/package for the NIH community, it provides maintenance, documentation, instruction, and assistance for users to interpret the results.

Statistical Systems/Packages Support. During this year, as in the past year, the Statistical Software Section of LSM maintained the following program packages and programs:

BMD, BMDP: Biomedical Computer Programs, UCLA.

SPSS: Statistical Package for the Social Sciences, SPSS, Inc.

SAS: Statistical Analysis System, SAS Institute, Inc.

P-STAT: Statistical Package, P-STAT, Inc.

IMSL: International Mathematical and Statistical Libraries, IMSL, Inc.

MSTAT1: Collection of Mathematical and Statistical Programs, DCRT.

During the year every system/package went through at least one major update. The SSS staff answered over 4,500 calls for assistance, and taught a total of eight courses on these systems/packages; two each on the SPSS and BMDP packages and four courses on the SAS system.

The use of program packages continues to increase. The average accesses per month of all the statistical packages rose from around 23,000 during FY80 to over 33,000 in FY81. For the fifth year in a row SAS experienced the largest increase of any of the packages. SAS averages over 24,000 accesses per month, up from 15,000 per month in FY81. The average number of accesses per month for SPSS increased from 5,500 to 6,000. The average

combined accesses of the BMDP and BMD packages rose from 1,700 accesses per month in FY80 to around 2,600 this year. As an example of a package used for specialized purposes, PSTAT averaged 60 accesses per month, down from 70 average accesses per month in FY80. The main programs and subroutines in MSTAT1 averaged 650 accesses per month, in contrast with 450 in FY80. Accesses to the IMSL package cannot be counted, but it is estimated that usage increased during FY81.

In addition, two new systems/packages were offered on an experimental basis to the NIH computer user community. SCSS, an interactive version of SPSS, and SAS/GRAPH, a graphics package from SAS Institute, were installed and tested at DCRT.

MLAB Support. The Biomathematics and Computer Science Section maintains the DECsystem-10 interpretive program MLAB for biomathematical modeling at NIH. This package, designed and implemented by BCS staff, is used by several hundred NIH researchers each year for various modeling and graphical display tasks. It has been sent to many universities and research centers at their request. It is part of the NIH-funded Prophet system, SUMEX-AIM at Stanford University, and the NIH-EPA Chemical Information System.

During FY81, a revision (Third Edition) of the *MLAB Applications Manual* was prepared and distributed. A series of tutorial articles on MLAB in *INTERFACE* continued this year, and six more articles have appeared. Two beginning MLAB courses and one advanced course were taught during FY81. MLAB was enhanced by improvements making it more efficient and by the addition of Fourier transform and inverse transform operations.

Support of C-LAB. SMS has assumed support of C-LAB, a computer system/package for pattern recognition and cluster analysis. A course on C-LAB was taught during the fiscal year. C-LAB techniques were modified to follow the latest published methods, and compatibility with MLAB was maintained.

Support for the Unified Generator Package. This package, developed by a BCS staff member, generates IBM S/370 assembly language programs. The compatibility of the package with new WYLBUR was maintained. As before, assistance was provided for users on request.

Support for REDUCE and PROLOG. BCS has continued support for the REDUCE system (obtained from the University of Utah) for manipulation of algebraic formulas.

The PROLOG software system (obtained from the University of Edinburgh) is used for non-numerical data processing. PROLOG has been applied in LSM research in linguistic analysis.

Indexing Program. An interactive DECSYSTEM-10 program for generating the index of a document file was completed. It is undergoing production testing on MLAB documentation now in preparation.

Consultation

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are successful, and are brief precisely because there is a known answer to the question posed. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

LSM consultations in FY81 were of the following types:

- Mathematical, statistical and computer science advice with limited computer use (5%).
- Mathematical or statistical advice with considerable computer use (55%).
- Computational advice alone (40%).

The large computer use in these figures results from the continued availability and use of general purpose statistical and mathematical packages like SAS and MLAB.

The diverse nature of LSM consulting is indicated by the projects and activities listed below.

Hemodynamic and Plasma Catecholamine Responses to Hyperthermic Cancer Therapy in Humans. Y. Kim (CC/ANES). Cancer patients treated by induction of hyperthermia under thiopental and fentanyl anesthesia, respond with attenuated hemodynamic changes compared with those reported on normal volunteers. Measured plasma catecholamine at hyperthermic condition showed evidence of sympathetic nerve response to hyperthermia. Statistical procedures used include multiple regression analysis, anova, and descriptive statistics.

Sleep Analysis. W. Duncan (NIMH/BDP). The analysis focuses on examining the relationship between mental illness and sleep disorders. Discriminant analysis was employed to evaluate possible contribution of sleep variables in distinguishing between groups of normal subjects and depressed (unipolar or bipolar) or insomniac patients.

Non-parametric Tests. W. Schneiderwind (CC). This study involves use of the non-parametric median and Mann-Whitney tests for comparing the effect of staff education on medical and patient care encounters.

Spectral Analysis of Mood Cycles. F. Putnam (NIMH). A frequency-domain spectral analysis study was done of possible connections between mood cycles and physiological measurements in disturbed patients.

Automatic Processing of Natural Language

Pathology Reports. D. Henson (NCI/BCPC). A data base for the Clinical Center surgical pathology data is being created using automatic encoding of natural language reports. An initial updating of the systematized Nomenclature of Pathology (dubbed SNOP-NIH) has been completed.

Automatic Encoding of Surgical Pathology

Reports. E. Jaffe (NCI/LP). In connection with the automatic encoding of surgical pathology reports, the new malignant lymphoma classification currently used at NIH was incorporated into SNOP.

Atlanta Autopsy Data Base. T. O'Leary (NCI/LP). The data and lexicographic changes consistent with SNOP were incorporated into the current Atlanta autopsy data base. Test runs were conducted.

Metal Ion Protein Binding. C. Chatterji (NIAID/LC). Optical absorbance experiments measured metal ion binding to a protein constituent of snake venom. LSM designed MLAB procedures to curve-fit mathematical models to the data.

Analysis of Simultaneous Binding Reactions. L. Jacobson (NICHD/LCP). Simultaneous binding reactions were studied by obtaining NMR scanner absorbances at specific frequencies. LSM assisted in mathematical modeling.

Ultracentrifuge Analysis. M. Lewis (DRS/BEI). A mathematical model was developed for studying the distribution of molecules in an organic solvent during ultracentrifugation. LSM assisted in model modifications to represent compressibility effects.

Compartmental Analysis of Drug Action. R. Burns (NIMH/LCS). Effects of drugs with radioactive tracers were studied in experimental animals. LSM

assisted in modeling drug action by developing a three-compartment differential equation system.

Interferon Measurements. M. Morin (DRS/VR). Groups of monkeys were injected with various compounds, and the yield of interferon was determined by measuring viral inhibition. Sample sizes required to produce significant differences between groups of compounds were calculated.

Potency Analysis. G. Krishna (NHLBI/IR CP). Maximum likelihood estimates of relative potencies of groups of compounds administered to a strain of mice were calculated. Log potency probit analysis techniques were applied.

Mapping Enzyme Cutting Sites on Circular Plasmid DNA. M. Huberman (NHLBI/MH). Specimen circular plasmid DNA is subjected to enzymes that cut the DNA at specific sites. Fragment lengths from one- and two-enzyme complete digest experiments are measured by electrophoresis. LSM designed and tested a pilot MLAB procedure to generate DNA maps consistent with the fragment data. An assessment of a Stanford computer program for constructing DNA maps from fragment data is scheduled for this fiscal year.

Continuous, Constant-Volume Diafiltration Methods. K. Roy (NIADDK/LMB). A laboratory technique for continuous, constant volume diafiltration measurements of binding parameters was designed and tested on several nucleic acid monomer-polymer systems. LSM assisted in modeling, designing, and testing of MLAB procedures. These procedures perform such functions as automatic elimination of bad data, curve-fitting of models to data, and generation of graphical displays of raw data, selected good data, and curve-fitted models.

K-means Clustering. J. Wunderlich (NCI). K-means clustering in CLAB was used to study the genetic control of immune response in mice, to identify high and low responders.

Depletion of Lymphocytes in Circulation. J. E. French (FDA/DBBP). Analysis of covariance was done for data pertaining to the depletion of circulating lymphocytes by leukapheresis in dogs.

Cell Microfilament Networks. N. Gershon (DCRT/PSL). Three-dimensional graphical displays of cell microfilament networks were prepared and presented at a scientific conference poster session. LSM assisted in using MLAB facilities for computer generation of three-dimensional graphical displays.

Free Run Cycling of Firefly Pacemaker. John Buck (NIADDK/LPB). The interflash duration of

fireflies was used as a measure of endogenous pacemaker timing behavior. Since Student's t-test, needed in analyzing free run pacemaking, requires that interflash durations have a Gaussian distribution, chi-square analyses of truncated samples were used to ascertain whether this requirement was fulfilled.

Protein Frequency Profiles. H. Saroff (NIADDK/LBP). Chi-square goodness-of-fit tests of the Gaussian, binomial, and Poisson distributions were applied to distributions of the number of random matches for amino acid sequences obtained from Monte Carlo experiments.

INSTITUTION DESIGNATION (Information Technology) PROJECT NUMBER (On NEI and NIH forms)		TITLE, RETIREMENT OF RESEARCH AND HUMAN SERVICES PROJECTS TO SERVICE INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT 00003-10 LSH
PERIOD COVERED October 1, 1980 through September 30, 1981				
TITLE OF PROJECT (80 characters or less) Automated Data Processing of Medical Language				
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT				
PI	R. G. Ragan	Computer Systems Analyst	L3M	NEI
	A. W. Pratt	Director	AD	DEB
Other	G. Dymish	Computer Programmer	L3M	DEB
	S. Harner	Computer Programmer	L3M	DEB
	J. Garcia-Hidalgo	Guest Worker	L3M	DEB
	W. Gratton	Guest Worker	L3M	DEB
COOPERATING UNITS (If any)				
None				
LABORATORY Laboratory of Statistical and Mathematical Methodology				
SECTION Medical Information Science Section				
INSTITUTE AND LOCATION DCST, NIH, Bethesda, Maryland 20205				
TOTAL PARTICIPANTS 2-5				
CHECK APPROPRIATE BOXES <input type="checkbox"/> (a) Human Subjects <input type="checkbox"/> (b) Human Tissues <input checked="" type="checkbox"/> (c) Neither				
<input checked="" type="checkbox"/> (a) <input type="checkbox"/> (b) <input type="checkbox"/> (c) <input type="checkbox"/> (d) <input type="checkbox"/> (e) <input type="checkbox"/> (f) <input type="checkbox"/> (g) <input type="checkbox"/> (h) <input type="checkbox"/> (i) <input type="checkbox"/> (j) <input type="checkbox"/> (k) <input type="checkbox"/> (l) <input type="checkbox"/> (m) <input type="checkbox"/> (n) <input type="checkbox"/> (o) <input type="checkbox"/> (p) <input type="checkbox"/> (q) <input type="checkbox"/> (r) <input type="checkbox"/> (s) <input type="checkbox"/> (t) <input type="checkbox"/> (u) <input type="checkbox"/> (v) <input type="checkbox"/> (w) <input type="checkbox"/> (x) <input type="checkbox"/> (y) <input type="checkbox"/> (z)				
SUMMARY OF WORK (200 words or less - see instructions)				
The major objective of the project is the development of methods for the automatic processing of natural medical language. A major application is the program for information storage and retrieval of pathology data for the Laboratory of Pathology, NCI. The entire corpus of surgical pathology will be encoded.				

(Please Print)

INSTITUTION DESIGNATION (Information Technology) PROJECT NUMBER (On NEI and NIH forms)		TITLE, RETIREMENT OF RESEARCH AND HUMAN SERVICES PROJECTS TO SERVICE INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT 00008-02 LSH
PERIOD COVERED October 1, 1980 through September 30, 1981				
TITLE OF PROJECT (80 characters or less) Cluster Analysis				
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT				
PI	M. S. Shapiro	Research Mathematician	L3M	DEB
	F. DeGennaro	Head	L3M	NEI
Other	S. Schein	Expert	L3M	NEI
COOPERATING UNITS (If any)				
None				
LABORATORY Laboratory of Statistical and Mathematical Methodology				
SECTION Biostatistics and Computer Science Section				
INSTITUTE AND LOCATION DCST, NIH, Bethesda, Maryland 20205				
TOTAL PARTICIPANTS 1-5				
CHECK APPROPRIATE BOXES <input type="checkbox"/> (a) Human Subjects <input type="checkbox"/> (b) Human Tissues <input checked="" type="checkbox"/> (c) Neither				
<input checked="" type="checkbox"/> (a) <input type="checkbox"/> (b) <input type="checkbox"/> (c) <input type="checkbox"/> (d) <input type="checkbox"/> (e) <input type="checkbox"/> (f) <input type="checkbox"/> (g) <input type="checkbox"/> (h) <input type="checkbox"/> (i) <input type="checkbox"/> (j) <input type="checkbox"/> (k) <input type="checkbox"/> (l) <input type="checkbox"/> (m) <input type="checkbox"/> (n) <input type="checkbox"/> (o) <input type="checkbox"/> (p) <input type="checkbox"/> (q) <input type="checkbox"/> (r) <input type="checkbox"/> (s) <input type="checkbox"/> (t) <input type="checkbox"/> (u) <input type="checkbox"/> (v) <input type="checkbox"/> (w) <input type="checkbox"/> (x) <input type="checkbox"/> (y) <input type="checkbox"/> (z)				
SUMMARY OF WORK (200 words or less - see instructions)				
Cluster analysis algorithms based on the latest published research and extensions to it were developed and tested.				
Algorithms for analyzing spatial point patterns were developed for testing patterns of retinal cones for regularity.				

(Please Print)

Research Projects

Automated Data Processing of Medical Language

The major objective of the project is the development of methods for the automatic processing of natural medical language. A major application is the program for information storage and retrieval of pathology data for the Laboratory of Pathology, NCI. The entire corpus of surgical pathology will be encoded.

The continued collaboration with the Laboratory of Pathology, NCI, to create a data base for the Clinical Center surgical pathology data indexed by automatic encoding has reached the following stage.

With Dr. Donald E. Henson (NCI/BCPC), the initial updating of the Systematized Nomenclature of Pathology (dubbed SNOP-NIH) was completed. This now permits indexing of almost all SNOP topographic descriptions found in the surgical pathology reports. The SNOP category of morphological diagnoses has been similarly updated for surgical pathology data. With Dr. Elaine S. Jaffe (NCI/LP), the new malignant lymphoma classification currently in use at NIH has been incorporated into SNOP-NIH.

The current surgical pathology data base has been automatically encoded, and some changes have been made in the automatic encoding program to reduce redundant and erroneous encoding.

This year, the Atlanta autopsy data base project was revived under the leadership of Dr. T. J. O'Leary, (NCI/LP). On the basis of test runs of these data, some lexicographic changes consistent with SNOP were incorporated into the current dictionary.

Work continued on the study of morphosemantic structuring of medical Greek-Latin derived forms. The goal is development of a generalized system for automatic morphosemantic analysis of medical compound words.

Work was elaborated on a project to determine automatically the productive morphemes (prefixes, infixes, suffixes) used in the formation of the terms appearing in the French translation of SNOP. The morphemes were isolated by procedures involving pairwise and setwise comparisons of terms. Nearly 17,000 terms were segmented.

An English-to-Spanish translation procedure and its associated dictionaries were developed and implemented for 1,426 terms of the morphology section of the International Classification of Diseases

for Oncology. Morphological substitutions and respelling rules permit translation of the ICD-O terms derived from Greek and Latin, which are cognate in the source and target languages, without construction of a large lexicon. This work was accomplished in cooperation with a guest worker, Isabel Garcia-Hidalgo.

The stem dictionary for the 'hepatitis' data base for NLM was completed.

A list of semantically productive terminal morphemes in medical language was prepared for the MEDLINE system at NLM.

Page copies of computer oriented medical dictionaries (SNOP, ICD) were made available to three medical institutions.

Future efforts:

- a. Continuation of research studies in medical language at present level (morphology, syntax, semantics).
- b. Creation of a lexicographic data base to be used for merging of medical dictionaries and extraction of microglossaries.
- c. Continuation of collaboration in the encoding of surgical pathology data with the Laboratory of Pathology, NCI, to refine the medical dictionary and study the language of diagnoses.

Publications:

Garcia-Hidalgo, I., and Dunham, G.: An experiment in English-Spanish automated translation of medical language data. *Methods of Information in Medicine* 20: 38-46, 1981.

Cluster Analysis

Cluster analysis algorithms based on the latest published research and extensions to it were developed and tested.

Algorithms for analyzing spatial point patterns were developed for testing patterns of retinal cones for regularity.

Background and Objectives: The main objective is the development of computer programs and methods for cluster analysis and related problem areas for use by NIH researchers.

Progress in FY81: New algorithms for representing multivariate data graphically have been programmed and will be added to the C-LAB cluster analysis package. These include Andrews plots, biplots, and probability plots. Recent work in the analysis of point patterns is being applied to the distribution pattern of cones from monkey retinas to determine if there is an underlying regularity and to measure the degree of regularity. Standard statistical tests indicate that

the distribution of cones is non-random, tending towards regularity.

Statistical methods, based on nearest neighbor distances between cones, were used to determine which type of regular pattern, with known error, is matched most closely. Voronoi regions (convex polygons surrounding each point) were computed and are being used as another approach to measuring regularity.

Proposed Course: Earlier work on measuring the effectiveness of cluster tendency algorithms will be completed.

More retinal cone data will be collected, and spatial distributions modeled, based on a statistical analysis of the data. A wider range of cluster analysis algorithms will continue to be developed and applied.

Publications: None

INSTITUTION: SCIENCE INFORMATION SYSTEMS PROJECT NUMBER: (DO NOT USE THIS SPACE)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC AFFAIRS DIVISION INFORMATION RESEARCH PROJECT		PROJECT NUMBER: Z01 CT 00077 OF LTM	
PUBLIC DATES: October 9, 1980 through September 30, 1981					
TITLE OF PROJECT (IN characters or less): Discrete Mathematics and Applications					
NAME, LAST NAME AND INITIALS, AFFILIATION, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI: G. Hutchinson		Research Mathematician		LTM JCCT	
Other: None					
COOPERATING UNIT: () ()					
DE(C)system-10 Systems Team, CCS, JCCT					
LABORATORY: Laboratory of Statistical and Mathematical Methodology					
SECTION: Biomathematics and Computer Science Section					
INSTITUTE AND LOCATION: DEPT. NEW, Bethesda, Maryland 20205					
TOTAL MANUSCRIPTS: 1		PROFESSIONAL: 1		OTHER: 0	
CHECK APPROPRIATE BOXES: <input checked="" type="checkbox"/> () HUMAN SUBJECTS <input checked="" type="checkbox"/> () HUMAN ISSUES <input checked="" type="checkbox"/> () WITHIN					
<input checked="" type="checkbox"/> () LATE REVISION <input checked="" type="checkbox"/> () INTERVIEW					
SUMMARY OF WORK (200 words or less - underline key words): Inclusion relations between vector spaces and related problems concerning modules over rings were studied. Preparation of scientific manuscripts by computer graphics methods using printer-plotters on minicomputers was investigated.					
PROJECT: (Date: 2-81)					

Discrete Mathematics and Applications

Inclusion relations between vector spaces and related problems concerning modules over rings were studied.

Preparation of scientific manuscripts by computer graphics methods using printer-plotters on minicomputers was investigated.

Project Description: The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics and graph theory), and to apply such methods to appropriate problems of biomedical research and computer science.

Methods Employed and Major Findings: Studies of inclusion relations between modules over a ring (a mathematical concept generalizing vector spaces and commutative groups) continued. A study giving five characterizations of the case that two rings have the same module inclusion theories (plus three more characterizations for finite rings) was completed and submitted for publication.

In computer science, previously developed minicomputer software for generating graphical displays of scientific and mathematical text was augmented. New facilities include: high-resolution hard copy output of scientific and mathematical text obtained using a Varian 9211 printer/plotter, direct incorporation of figures and graphs generated on the DE(C)system-10 using MLAB or OMNIGRAPH into pages of scientific text, and many new notations and character fonts implemented. It is expected that the first complete version of this system will be available during this fiscal year. Parallel with this work, the computer program TEX developed at Stanford University for computer generation of mathematical text was adapted for NIH by the Laboratory Systems Unit. Experimental trials have used TEX to generate mathematical text on the printer/plotter.

Proposed Course: Study of the equivalence of different approaches to module theory will be continued. The most important unsolved problem is the classification of rings that lead to the same restricted theory of modules.

Research on computer generation of scientific manuscripts will continue, with most work concentrated on improvement of computer input methods so that mathematical notations can be described without placing heavy burdens on the users. Experimental work involving the TEX system will continue.

Publications:
 Hutchinson, G. A complete logic for n -permutable congruence lattices
Algebra Universalis (in press)

INFORMATION SYSTEMS INFORMATION EXCHANGE PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE OFFICE OF INFORMATION RESEARCH PROJECTS	PROJECT NUMBER Z01 ET 00087-03 15M
FUNDING PERIOD October 1, 1980 through September 30, 1983		
TITLE OF PROJECT (40 characters or less) Non-numerical Programming Techniques and Applications		
NAME, LOCATION AND INCLUDE AFFILIATION, AND TITLE OF PRINCIPAL INVESTIGATOR, AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT		
PI (Other)	L. M. Norton None	Research Mathematician LOM DORT
COOPERATING UNIT, (If any)		
None		
LABORATORY Laboratory of Statistical and Mathematical Methodology		
DIVISION Biostatistics and Computer Science Section		
INSTITUTION AND ADDRESS DORT, NIM, Bethesda, Maryland 20205		
OTHER ADDRESS (If any)	(If any)	(If any)
SOURCE OF FUNDING (If any)	<input type="checkbox"/> (a) FEDERAL <input type="checkbox"/> (b) NON-FEDERAL <input checked="" type="checkbox"/> (c) NEITHER	(If any)
SUMMARY OF WORK (200 words or less - narrative required) The special-purpose computer language PROLOG is being used to explore a potential research project in computational linguistics and artificial intelligence. The ultimate goal of this project is to develop a methodology for automatically transforming the information presented in a textbook into a form which may be used in an appropriate manner by a computer.		
PROJECT (Rev. 2-81)		

Non-numerical Programming Techniques and Applications

The special-purpose computer language PROLOG is being used to explore a potential research project in computational linguistics and artificial intelligence. The ultimate goal of this project is to develop a methodology for automatically transforming the information presented in a textbook into a form which may be used in an appropriate manner by a computer.

A textbook on BASIC programming has been chosen and a heavily edited version of its first chapter has been used to avoid numerous problems of computational linguistics not directly relevant to the specific task of manipulating knowledge representations. To date, a PROLOG program has been developed that can analyze an input of three paragraphs in English that describe how to write expressions in the BASIC language. As a result of analyzing these paragraphs, the PROLOG program automatically synthesizes a program that could determine whether or not strings of characters form legal BASIC expressions. The use of PROLOG is essential to this project. It is appropriate for tasks in computational linguistics and artificial intelligence, and for the representation of knowledge (particularly procedural knowledge) as well.

A paper has been prepared which discusses the aims, methods, and initial progress of this project.

Publications:

Norton, L. M.: A note about Laplace transform tables for computer use.
SIGSAM Bulletin 14: 30-31, 1980.

INTERNATIONAL RESEARCH INSTITUTIONS (CONTRACTS) PROJECT NUMBER (DO NOT USE THIS SPACE)	FULL DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE INTERNATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 T-00074-01 (1/84)
PERIOD COVERED October 1, 1980 through April 30, 1981		
TITLE OF PROJECT (40 characters or less) Topics in Geometry and Analysis		
NAME, LABORATORY AND INSTITUTE AFFILIATION, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: M. A. O'Connor, Ph.D., Staff Fellow I M DCRT		
COOPERATING UNIT (If any) None		
LABORATORY Laboratory of Statistical and Mathematical Methodology SECTION Biomathematics and Computer Science Section INSTITUTION AND LOCATION DHEW, NIH, Bethesda, Maryland TOTAL BUDGETED 0.3 FUNDING AGENCY NIH		
OTHER APPROPRIATE SUBJECTS <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) MICROBES <input type="checkbox"/> (d) MINES <input type="checkbox"/> (e) CATALYSIS SUMMARY OF WORK (200 words or less - underline key words)		
Metrics for convex homogeneous cones were studied. A mathematical formalism for the symmetric axis transform is under development.		

Topics in Geometry and Analysis

Metrics for convex homogeneous cones were studied. A mathematical formalism for the symmetric axis transform is under development.

Progress in FY81: Four invariant (under the group of linear automorphisms) metrics on convex homogeneous cones have been studied. Bounds on those have been obtained, and an equivalent expression for each has been found, which allows its explicit calculation in a simple closed form involving generalized 'eigenvalues' of the cone's Vinberg algebra representation. A parametrization of an interesting family of cones has been obtained, which offers the possibility of applications to the generalized symmetric spaces, and further study of this has been initiated.

A mathematical formalism for the symmetric axis transform is being developed. The techniques involved allow generalizations from open sets in two-dimensional Euclidean space to open sets in n -dimensional Euclidean space and the study of convergence properties of symmetric axis transforms. By methods analogous to those used in cut sets of Riemannian manifolds, topological invariants of the manifold have been shown to be inherited by its symmetric axis. A study of local differential geometric properties of the axis has been initiated.

Publications:

O'Connor, M. A. Invariant metrics on cones. *Proc. of the Conference on Invariant Metrics and Holomorphic Maps* Rome, Italy, Istituto di Alta Matematica F. Severi di C.N.R. (in press)



Computer Systems Laboratory

Alan M. Demmerle, Chief

Summary of Activities

Computer Support for Flow Microfluorimetry/Cell Sorters[FMF] (NCI, NHLBI). This project provides support for acquisition and processing for four Becton-Dickinson FACS II and one Coulter instrument. Of these, three were new in FY81. FACS II/PDP-11/34 systems were installed for IR, EA, NHLBI and EEB, NCI. A Coulter PDP-11/34 system was installed for VA MOB, NCI. All CSL systems are currently using DEC's RT-11 single user operating system. CSL is developing an RSX-11M multi-user system to replace RT in some high volume applications. This system will feature an LSI-11 microcomputer that will independently interact with the FMF operator during parameter entry and will acquire data. Benchmark testing and design of the LSI-11 buffer was accomplished in FY81. Both the RT and RSX systems use DEC's VT-11 graphics terminal, which is no longer available for purchase and on which guarantee maintenance is scheduled to be eliminated. After a thorough evaluation, a Tektronix T4025 was selected as a replacement. CSL is pursuing a contract to develop software to respond to the existing VT-11 graphic calls and drive the T4025.

Cardiac Scintillation Probe(NM, NHLBI). CSL has continued the development of its Cardiac Scintillation Probe System begun in 1977. This non-imaging ECG-Gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. Derived parameters such as LV compliance can also be monitored, in addition to such measurements as ejection fraction, filling and ejection rates, and temporal relationships. This year realtime pressure-volume measurements were used to study the effects of nifedipine and verapamil on patients with asymmetric septal hypertrophy. New hardware and software have been developed to allow online calculation of new parameters and permit the system to be easily used on a routine basis by the Clinical Center personnel. Development is continuing to increase the detection efficiency of the probe and to quantify the limitations of the technique.

Nuclear Medicine Computer Systems(CC). CSL has continued consultation and support for the imaging systems located in the Nuclear Medicine Department. This involved working with Nuclear Medicine to assess their clinical computing requirements in regard to their changing needs and anticipated growth with the new Ambulatory Care Research Facility. This year, due to the increased demand for routine clinical cardiac studies, the Nuclear Medicine Department has doubled the capabilities in this area by purchasing an additional camera system and expanding its computer system. CSL helped specify a camera system that, in addition to performing present cardiac studies, would permit the investigation into high efficiency camera systems and their potential applications.

Computerized Radiation Therapy(NCI). CSL has developed a computer system, now in clinical operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from computer assisted tomography to improve radiation treatment planning. This system for external beam treatment planning is based on a generalized 3-D dose field model that covers photon, electron, and neutron beams.

The computer program and most of its clinical implementation has been completed for the photon and electron fields available from the local 6 MV and 12 MV linear accelerators. The current capabilities include interactive simulation of most irradiation techniques, including the effect of most beam modifying devices. The system enables the display of dose distributions computed in several transverse contours and overlaid on corresponding CT scans.

Cardiac Intensive Care Unit Patient Monitoring Computer System(NHLBI). The Surgery Branch of NHLBI has collaborated with CSL on a continuing basis in the development of automated techniques for monitoring patients in a post-operative cardiac intensive care environment. Previous annual reports describe the details of the system's functional goals and project milestones. The system was maintained in continuous operation until the end of December when the computer was removed from service, in

anticipation of the Surgery Branch's pending relocation to new facilities in the Clinical Center. The new Intensive Care Unit, constructed this year, had been planned with the design features necessary to support computerization. The decision as to which of several approaches to online patient monitoring is to be implemented will be deferred until next year.

Medical Intensive Care Unit Patient Monitoring Computer System(CC). Automation of the Medical Intensive Care Unit required the development of a multiple-computer system configuration to provide for the measurement, analysis, control, and recordkeeping functions that are dictated by the role of the unit. The departure of the unit's senior staff at the end of last year resulted in the temporary cessation of hardware/software development, although the system was maintained in continuous operation. With the arrival of a new Department Chief, a reconsideration of system goals was undertaken. Particular emphasis was placed on upgrading the system's cardiac catheterization capabilities. Data collection and retrieval functions of the primary patient data management system are being reconfigured to support anticipated research protocols.

The Biomedical Image Analysis Project(NHLBI, NEI, NCI, NIDR, NIADDK). This project is oriented toward the development of general-purpose algorithms and techniques for image digitization, contrast enhancement, edge detection, contour extraction, contour following, contour coordinate data compression, and three-dimensional representation. The resultant general-purpose capability is being accomplished through work with a number of NIH researchers who encounter relatively similar classes of problems in unique individual settings.

Automated Electrocardiogram Processing System(CC). A computer system for the online collection, analysis, storage, and retrieval of diagnostic electrocardiograms was procured this year to automate the Clinical Center's Heart Station. The system was installed in refurbished facilities at the site of the dismantled cardiac intensive care unit patient monitoring computer system, and acceptance testing was rapidly completed. The delivery and installation of special NIH-specified software paralleled the training of the operational staff and the education of all clinical center physicians regarding the switchover to the automated electrocardiogram system.

Molecular Graphics(NIDR). Three projects use the Evans and Sutherland Picture System for modeling of protein structures.

1. From the amino acid sequence of collagen, detailed structures can be analyzed and compared with x-ray diffraction and electron microscopy data.

2. As the amino acid sequence of the helical portion of myosin is obtained from cyanogen bromide fragments, these pieces can be modeled as double stranded alpha helices. When the complete sequence is known, more sophisticated models including groups of molecules can be designed.

3. A study of the structure and possible models of streptococcal M proteins is also underway in collaboration with the Rockefeller University. These models are based on a double stranded alpha helix.

Rehabilitation Medicine Department Computer System(CC). This project involves the development of computer techniques in rehabilitation medicine in collaboration with the Rehabilitation Medicine Department of the NIH Clinical Center. CSL has recommended computer techniques that can be used to automatically acquire anatomical and physiological information from patients, perform calculations on the data obtained, and display the necessary results to the medical staff. The automated techniques include the measurement of body forces (hand and ground reaction forces), muscle activity (monitoring the electromyogram of muscles), and body kinematics (the position and angles of the limbs and joints in space and time). The system will also allow the medical staff to access a data base with computer generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data. In FY82 CSL will continue the work begun in FY81 including the specification of the computer system, the evaluation of methods to perform the desired measurements, the selection of the necessary transducers and instrumentation, and the specification of the required software.

Automated Pulmonary Physiology Testing(NHLBI). Lung compliance and inspiratory muscle strength procedures performed in the pulmonary physiology/exercise laboratory of the Pulmonary Branch have been automated using a MINC 11/03 computer system. Data is acquired and analyzed in realtime, with graphical and textual reports being produced at the completion of each procedure. An exercise testing procedure has been partially automated. Data from the test is entered into the computer manually. Analysis and report generation are then completed automatically by the computer. Work is in progress to enable automatic realtime acquisition of exercise data. A scheme has been developed to locally store patient results from the above tests on disk for retrospective reference.

Eventually, this data will be transmitted to the central PB data base scheduled for development by the Data Management Branch.

Pulmonary Branch Support(NHLBI). This project involves assisting the Pulmonary Branch to meet its computer and data processing needs. CSL has helped to maintain the computer portion of the two automated pulmonary function analyzers installed last year. Cooperation with DMB resulted in a proposal accepted by PB for DMB to develop a clinical data base. During FY82, we expect the data base system to be completed. We will interface both the automated pulmonary function analyzers and the pulmonary physiology computer (reported separately) to it.

Computer Interfaces for Clinical Laboratory Instruments(CC). Efforts were continued this year to improve the acquisition and reporting of clinical laboratory test results. A second Coulter Model S-Plus cell counter was connected to the Clinical Laboratory Computer System using the method designed in FY80. Development of a multistation microcomputer system for white cell differential counting, started in FY80, was also continued this year. The system will support up to eight stations and will be connected directly to the Clinical Laboratory Computer System. In addition to differential counting, technologists will be able to use the system to access and review Coulter results. Testing of a single station prototype system is complete; the full system should be operational early in FY82.

Distributed Laboratory Data Acquisition and Control System(NIADDK). A Distributed Laboratory Data Acquisition and Control System (DLDAACS) has been implemented for NIADDK, in Building 2, as a replacement to the Laboratory Computer System developed by CSL ten years ago. The new system consists of a network of remote microcomputers connected in a star configuration through a communications processor to a central data processing computer. The remote microcomputers handle all of the realtime data acquisition requirements and provide instrument control functions when required. The collected data is normalized, buffered, and transmitted at a convenient time to the communications processor as files over a serial line, using a standard block communications protocol. The communications processor serves as a store and forward front end for the central computer. Currently there are seven satellites connected to the system supporting ten instruments which includes four added this year. Presently the system is configured with two host

processors, a Honeywell-516 and a DEC PDP-11/70, connected to the communications processor allowing a staged transition of processing programs from the H-516 to the PDP-11/70.

Molecular Interactions Laboratory Data System(NHLBI). This microcomputer (PDP-11/03) data system supervises the acquisition and processing of information from an ultracentrifuge and a circular dichroic spectropolarimeter used in MDB, NHLBI to investigate the interactions between human lipoprotein subunits. Current capabilities include acquisition, display, and preprocessing of data from the ultracentrifuge and transfer of preprocessed data files to the DECsystem-10 for further analysis. The characterization of interacting systems is then carried out under MLAB on the DECsystem-10. Computation of molecular weights for both associating and non-associating systems are also performed under MLAB. An interface to the CARY 61 spectropolarimeter was designed, fabricated and tested in FY81. Software support includes the ability to add, subtract, and average CD spectra and to transfer files to the PDP-10 for further analysis.

Californium-252 Plasma Desorption Mass Spectrometer Data System(NHLBI). The Californium-252 plasma desorption mass spectrometer puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Realtime performance and the ability to access very large data arrays in main memory are key considerations. A data system design modeled after one in use at Texas A & M University has been purchased and will be operational soon. Special interface electronics and stepping motor controllers for automatic tuning are under construction in CSL.

Combined EDS-WDS X-Ray Analysis Scanning Electron Microscope System(NIADDK). This Project entailed the development of a scanning electron microscope system capable of simultaneously analyzing the x-ray emissions of a sample under observation by both energy-dispersive and wavelength-dispersive detectors. The system permits localization and quantitation of both light and heavy elements in the sample, storage of raw and reduced data within the data system, processing of data, and transmission of data to a remote DECsystem-10 computer system at DCRT. This system is complete and no further development is anticipated.

Radiation Counter Data Recorder. A six-month extension was negotiated for the contract awarded in

FY80 for the manufacture of Radiation Counter Data Loggers. Under this extension NIH investigators could purchase Data Recorders using a Record of Call. NIH purchased 18 Data Recorders under this extension. Since the response was small, a new contract will not be sought. NIH laboratories can continue to order Data Recorders using a standard requisition (NIH-402). CSL continues to assist laboratories in converting their liquid scintillation and gamma counter data outputs to Data Recorder systems, and in overcoming related data communications problems.

Measurements of Transepithelial Resistance of Kidney Tubules(NHLBI). A microprocessor-based instrument was developed in FY80 to facilitate the determination of the transepithelial resistance of an in vitro preparation of kidney tubule. The instrument was upgraded this year to include the online calculation of the tubule resistances and other parameters of interest using a complex set of equations derived from a transmission line model. Floating-point hardware was added to the instrument along with the software to utilize it. This new function provides the investigator with immediate feedback about the course of the experiment.

Electron Microanalysis Facility(DRS). CSL in collaboration with DRS/BEIB is developing an automated electron microanalysis facility consisting of two electron microscopes interfaced to a PDP-11/60 computer system. The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL is designing and implementing the computer system, which will acquire and display the spectra and images resulting from Electron Energy Loss and x-ray spectrometry. This year, software was developed for defining specimen target areas, for acquiring EELS and EDS spectra and electron current signals while scanning the target, and for acquiring, calibrating, monitoring, and displaying 'housekeeping' parameters. Work was begun on software for the DeAnza Color Display System and for retrieving empirical x-ray information.

Metabolic Energy Measurements(NHLBI). This project is directed toward the development of new and improved instrumentation and techniques for the study of energy transfer at the cellular level. In FY80 a microprocessor based system was designed to study energy parameters of respiring membranes and this year the system was made operational. Electrodes are used to measure concentrations of specific ions as well as those of protons and of oxygen. The membrane potentials measured by these new techniques agree with those determined

by traditional methods.

Bioassay Information System(NCI/NTP, NCTR/FDA). Through an interagency agreement, the National Center for Toxicological Research (NCTR) of the Food and Drug Administration is developing a computerized data base system for the NCI Bioassay Program using the NCTR Toxicology Data Management System (TDMS). The NCI Bioassay Program involves the testing of chemicals with animals for the detection of carcinogens by contract laboratories located at many sites around the country. A goal of this project is to automate the acquisition of the animal data at the laboratory sites and to transmit this data to a central computer so the data can be used to monitor the progress of all tests and to evaluate test results. Since FY77 CSL has served as a consultant to NCI specifying and evaluating hardware and software components of this system.

During FY81, the terminal contractor delivered thirty of the microcomputer-based programmable data acquisition terminals to NCTR in Arkansas for final testing before being shipped to the laboratory sites. Five of these terminals were shipped to Southern Research Institute, Birmingham, Alabama, the first bioassay laboratory location chosen for automation. CSL has monitored the contractor performance on providing the hardware and software components of the terminal. Another terminal was shipped to NCI, Bethesda, Maryland and was used by CSL to establish and test a high speed (4800 baud) synchronous communications link with the NCTR IBM computer facility in Arkansas using a communications protocol emulator software package provided by the contractor. This link will be used by the bioassay laboratories in the future to transfer files with NCTR. CSL also reviewed a report written by three outside consultants evaluating the entire TDMS. CSL expects to continue its consulting role which includes the evaluation of possible new configurations for this computer network.

Small Animal Section Data Base Management System(DRS). The Small Animal Section of the Veterinary Resources Branch requires a data base system to facilitate the data entry, record keeping, and report generation associated with animal breeding and distribution. CSL has concluded an in-depth study of the Small Animal Section operations and has composed the functional specifications for a system that will satisfy the needs of the SAS. From these specifications we anticipate releasing one or more Requests for Proposals early in FY82 to cover requirements for a total system to manage the data associated with breeding, ordering/inventory control,

quality control, and genetic resources. No known system currently exists that will meet all of these requirements.

Voice Output Terminal for the Blind. The voice output terminal design was first made operational in FY79 and has proved to be a valuable asset to the blind computer professional. Voice output terminals are now available from several vendors. Two of these are based on original CSL work. We are collaborating with our blind users to develop ways of presenting complex text formats--tables, forms, etc.--in audible form. This should make voice output devices useful to a wider segment of the blind community.

Library Automation Project(DRS). This project is directed toward automating the major functions of the NIH Library. In response to the CSL study reported on in FY79, the NIH Library has decided to purchase the available elements of an automated total Library system. As no currently procurable system is expected to meet all NIH Library specifications, CSL plans to adapt a purchased system to unique Library requirements. CSL exhaustively studied Library needs and generated a comprehensive 'Request for Proposals' covering hardware, software, and conversion of Library holdings to machine readable form in FY80. The Library system procurement was delayed one year for administrative reasons. During the last year, CSL developed a cost-benefit analysis for the Library system and updated the RFP to reflect the improvements in the available systems. System installation is anticipated for late Summer 1982, at which time CSL's development effort should be underway.

Image Processing Facility. This project is intended to provide a utility to display and analyze digital images. The system will consist of a powerful 32-bit computer with a mixture of medium and high resolution video displays. Also, the system will include a microdensitometer to allow precise digitization of x-rays, micrographs, and other images. The computer and peripherals have been purchased, with delivery expected during the next fiscal year, and the design for physical space to house the system is complete. Construction will begin soon, with completion expected during the next eight months. The display subsystem specifications are complete, and procurement is expected during the next year.

Medical Information Technology Project. This project is concerned with developing improved man-machine interface methods such that modern microprocessor technology can better serve the

needs of physicians and the practice of medicine.

This year we have started to field test some of the concepts developed in previous years. We have created a friendly assistive environment, which allows a dermatologist to create and retrieve the full spectrum of data contained in a patient record. With a minimum of keystrokes the examining physician can select and simultaneously record from a set of choices for diagnosis, symptoms, signs, procedures, tests, and prescriptions. We have chosen the most frequent dermatologic disorders, encompassing over half of all patient visits, as a basis for this pilot study. Advantageous techniques that result from this study will be applied to other clinical and research recording situations.

Computers in Cardiology Conference. CSL has continued its support of the annual International Conference on Computers in Cardiology. The conference provides a forum for direct interaction and exchange between physicians, computer scientists, and engineers who are involved in various aspects of clinical systems in the field of cardiology. CSL was responsible for planning and organizing the 1980 Conference in Williamsburg, VA, and helped edit the Proceedings. This year, six pre-conference tutorials were organized. Each tutorial is designed to introduce its subject area to those who are unfamiliar with it. Participants who need an introduction to the computer aspects of a subject area or those with computer experience who need an introduction to the medical aspects of a subject area are encouraged to attend. This year's Conference was attended by 300 people from 14 countries.

INTERVIEW (SEEK INFORMATION EXCHANGE) PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00054-02 CSL
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (40 characters or less) Computer Support for Flow Microfluorimetry/Cell Sorters (FMF)		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED ON THE PROJECT		
PI: Robert J. Romanoff Computer Specialist CSL, DCRT OTHER: Ronald Fico Electronics Engineer CSL, DCRT Irving Levy Electronics Engineer CSL, DCRT Lee W. Freeman Computer Programmer CSL, DCRT Eric S. Loiedeman Computer Aid CSL, DCRT Arthur R. Schultz, Jr. Chief, Processor Design Section CSL, DCRT Susan D. Sharrow Chemist I, NCI		
COOPERATING UNITS (if any) I, NCI: LP, NCI: EEB, NCI: VA MOB, NCI: EA, NIMB1		
LAB/BRANCH Computer Systems Laboratory		
SECTION Processor Design Section		
ADDRESS AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANHOURS 4.0 PROFESSIONAL 3.7 OTHER 0.3		
OTHER APPROPRIATE NOTES <input type="checkbox"/> (a) human subjects <input type="checkbox"/> (b) human tissues <input checked="" type="checkbox"/> (c) neither <input checked="" type="checkbox"/> (d) animals <input type="checkbox"/> (e) infectious <input type="checkbox"/> (f) neither Summary of data (200 words or less - underline key words) This project provides PDP-11 computer support at various levels for four Becton-Dickinson FACS II Flow Microfluorimeter (FMF/Cell Sorters) and one Coulter MDADS FMF. Data display and analysis for high sample throughput is the principle system feature. Software currently running under the RT-11 operating system is being converted to function under the RSX-11M operating system in order to allow more sophisticated recordkeeping and more effective support of current and anticipated workloads. New hardware and software capabilities are being added during the conversion effort.		

PHS-603
(Rev. 2-81)

INTERVIEW (SEEK INFORMATION EXCHANGE) PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00054-02 CSL
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (40 characters or less) Distributed Laboratory Data Acquisition and Control System		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED ON THE PROJECT		
PI: John Powell Physicist LCP, NIAID/DCRT OTHER: William Jennings Electronics Engineer LCP, NIAID/DCRT Ronald Fico Electronics Engineer CSL, DCRT Eugene D'Bryan Electronics Engineer CSL, DCRT Arthur R. Schultz, Jr. Chief, Processor Design Section CSL, DCRT		
COOPERATING UNITS (if any) LCP and LMB, NIAID/DCRT		
LAB/BRANCH Computer Systems Laboratory		
SECTION Processor Design Section		
ADDRESS AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANHOURS 3.0 PROFESSIONAL 3.0 OTHER		
OTHER APPROPRIATE NOTES <input type="checkbox"/> (a) human subjects <input type="checkbox"/> (b) human tissues <input checked="" type="checkbox"/> (c) neither <input checked="" type="checkbox"/> (d) animals <input type="checkbox"/> (e) infectious <input type="checkbox"/> (f) neither Summary of data (200 words or less - underline key words) A local computer network has been developed for LCP and LMB, NIAID/DCRT in Building 2 at the National Institutes of Health (NIH) as part of an integrated laboratory data acquisition and processing system. This network is configured with satellites connected in a star configuration to a host processor. At each satellite a dedicated microcomputer system performs data acquisition from and control over an instrument/experiment. Although acquired data files may be stored locally, they are normally transferred via the network to a host storage medium. The hub of the network, the concentrator, utilizes DMA hardware on all communicating links and performs a file store and forward function. The local network allows the host storage medium to appear as a "virtual" storage device to the satellites.		

PHS-603
(Rev. 2-81)

Research Projects

Computer Support for Flow Microfluorimetry/Cell Sorters (FMF)

This project provides PDP-11 computer support at various levels for four Becton-Dickinson FACS II Flow Microfluorimeter (FMF)/Cell Sorters and one Coulter MDADS FMF. Data display and analysis for high sample throughput is the principle system feature. Software currently running under the RT-11 operating system is being converted to function under the RSX-11M operating system in order to allow more sophisticated recordkeeping and more effective support of current and anticipated workloads. New hardware and software capabilities are being added during the conversion effort.

Background and Objectives: Since FY75, CSL has provided engineering, system integration, and software support necessary to meet the data acquisition, data display, and analysis needs of several investigators using Flow Microfluorimeters (FMF's) at NIH.

In FY81, CSL continued to support a FACS-II/PDP-11/34 FMF system for I, NCI and a similar system for LP, NCI. LP, NCI replaced their Los Alamos Scientific Laboratory FMF with a FACS-II in FY80. Two new FACS-II/PDP-11/34 systems were installed in FY81 with CSL assistance. These are located in EA, H and EEB, NCI. CSL also assisted in installing and making software modifications for a Coulter MDADS/PDP-11/34 system located at the VA Hospital in Washington, D.C. for VA MOB, NIC. All CSL supported systems are currently using the RT-11 single-user operating system.

Progress in FY81: The major software effort in FY81 was continuing the conversion of RT-11 programs to run under the RSX-11M multi-user operating system as well as adding functionality to these programs. The RSX-11M system is being developed to replace RT-11 in selected CSL-supported systems in order to provide more effective support of current and anticipated workloads and more sophisticated data acquisition and record keeping functions. In FY81, a multi-level report generation program for FMF data file information was developed, as was a more efficient driver program for ZETA 1553 incremental plotters. Improvements were also made to the data display and analysis programs.

Currently, both the RT-11 and RSX-11M systems use the Digital Equipment Corporation (DEC) VT-11 as the graphics display device. The VT-11 is no longer available for purchase and DEC will not provide guaranteed maintenance after three additional years.

After a thorough evaluation of available devices, CSL selected a new graphics terminal, a Tektronix T4025, initially for RSX-11M use and eventually for RT-11 use. During the third quarter of FY81, CSL was pursuing a contract to develop software packages that will respond to the existing VT-11 graphics calls and drive the T4025 under both RT-11 and RSX-11M.

In order to deal with the degradation of data acquisition speed under RSX-11M, it was decided to develop an LSI-11 microcomputer-based data acquisition system that will independently interact with the FMF operator during parameter entry and send the acquired data to the host PDP-11/34 RSX-11M system over an interprocessor link. An important feature of the LSI-11 will be the ability to create a 'laboratory notebook' as a permanent hard copy rather than continuing this as a manual task. Considerable benchmark testing and design of this system was accomplished in FY81 and appropriate hardware was ordered.

Several minor improvements to the RT-11 display and analysis programs were made in FY81 in order to accommodate immediate needs of our users.

Also, an efficient program to interface RT-11 to the ZETA 1553 incremental plotter was written and installed. The ZETA 1553 plotter replaced the Houston Instruments plotter on all CSL-supported systems in FY81.

During FY80, a contract was negotiated to provide four FMF hardware interfaces. These were delivered, tested, and installed during the third quarter of FY81.

CSL has also responded to many external requests and has provided copies of the interface hardware schematics, software, and documentation to FMF sites in the U.S., Europe, and Australia.

Proposed Course: In the forthcoming year, CSL plans to complete the first RSX-11M-based FMF system and LSI-11-based data acquisition system and put them into operation at the I, NCI facility. If resources permit, the RT-11 software will be rewritten to use the T4025 graphics terminal as a replacement for the VT-11.

Distributed Laboratory Data Acquisition and Control System

A local computer network has been developed for LCP and LMB, NIADDK, in Building 2 at the National Institutes of Health (NIH) as part of an integrated laboratory data acquisition and processing system. This network is configured with satellites connected in a star configuration to a host processor. At each satellite a dedicated microcomputer system performs

data acquisition from and control over an instrument/experiment. Although acquired data files may be stored locally, they are normally transferred via the network to a host storage medium. The hub of the network, the concentrator, utilizes DMA hardware on all communicating links and performs a file store and forward function. The local network allows the host storage medium to appear as a 'virtual' storage device to the satellites.

Background and Objectives: A system of microcomputers capable of independently controlling and acquiring data from an instrument/experiment was proposed in December 1976 as the best system architecture of upgrading laboratory data processing. A prototype laboratory data acquisition and control (LDACS) computer and the essential elements of the communication system were developed.

Satellites perform the realtime data acquisition and instrument control functions. Their configuration includes a Digital Equipment Corporation (DEC) LSI-11 microcomputer, 28K words memory, low density random access storage, graphics terminal, and all the necessary I/O hardware to interface the instrument/experiment. Satellite software runs under DEC's RT-11 realtime operating system. A hardwired serial link connects a satellite to the concentrator. Although each satellite is capable of stand-alone operation, the immediate transfer of the files allows data processing to proceed on the host system simultaneously with data acquisition on the satellite system. The host processor, a DEC PDP11/70, is configured with: 128K words of memory, a high speed printer/plotter, a 9-track magnetic tape drive, and two large capacity disc drives. DEC's multiuser, multitasking operating system, RSX-11M, is used to service the processing needs of the users. User access to the host is provided by hardwired links between terminals and host timesharing ports. Instruments previously reported as being connected to the network include: Spectrophotometers; CARY 118, Perkin Elmer 580B, CARY 14; Spectropolarimeter, CARY 60; Electron spin resonance spectrometer; Varian; and a stimulus response retina experiment.

Progress in FY81: Seven satellites supporting ten instruments are currently connected to the system. Four instruments added this year include a CARY 219 spectrophotometer, a microspectrophotometer designed by NIADDK, a Jasco J500A spectropolarimeter, and a I.S. Co. Model 1440 liquid chromatograph.

Presently, the system is configured with two host processors, a Honeywell-516 and a DEC PDP-11/70.

The H516 is the data acquisition and processing computer from a 10-year old centralized system in NIADDK. Having both host processors available allows a gradual transition of processing functions from the H-516 to the PDP-11/70.

In addition, a multipurpose counter/timer module was developed for use with LDACS and software was provided for the CARY 118 LADACS to accommodate a new experimental technique for measuring absorbance versus concentration.

CSL had the first part of a two-part users manual written under contract. This 60-page document is intended as a guide to introduce scientists to the system and the LDACS functions and utilities that are common to all instruments. The second part of the manual will be specific for each LDACS and will describe unique instrument related functions.

Proposed Course: Support for the system will continue. Additional software to further utilize systems capabilities will be provided for the Jasco J500A, the Perkin Elmer 580B, the CARY 219, and the microspectrophotometer. Earlier LDACS software will be modified as necessary to incorporate the software libraries and modules that have now been standardized for LDACS. Documentation of the system will be given a higher priority, with the objective of completing an LDACS users guide for each LDACS and of documenting the common software libraries developed for LDACS.

Publications:

Powell, J. I., Fico, R., Jennings, W. H., O'Bryan, E. R., Schultz, Jr., A. R.: A Local Network for Distributed Laboratory Microcomputer. *Proceedings of the Twenty-first IEEE Computer Society International Conference*. September 1980, pp. 185-190.

THE JPL PLAN (JPL) OF INFORMATION EXCHANGE
PROJECT NUMBER (JPL 000) AND JPL NUMBER
JPL PLAN NUMBER (JPL 000)
JPL PLAN NUMBER (JPL 000)
INTERNATIONAL RESEARCH PROJECT

PROJECT NUMBER
Z01 C100058-02
CSL

PERIOD COVERED
October 1, 1980 to September 30, 1981
TITLE OF PROJECT (40 characters or less)

Californium-252 Plasma Desorption Mass Spectrometer Data System

TITLE, LOCATION AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PARTICIPATING PERSONNEL ENGAGED IN THE PROJECT

PI: Raman L. Tate, Ph.D. Computer Specialist CSL, DCMT
Other: Henry Fries, Ph.D. Chief CSL, NERL

LABORATION
Computer Systems Laboratory

TITLE
Processor Design Section

PARTIAL TITLE AND LOCATION
DCMT, NERL, Bethesda, MD 20205

STAFF NUMBER
0.2

PROFESSIONAL
0.2

SENIOR
0.2

OTHER APPROPRIATE ROLES
☐ (a) human tissues ☐ (b) human tissues (c) neither

☐ (d) windows ☐ (e) interface

SUMMARY OF WORK DONE (200 words or less, including references)

The Californium-252 plasma desorption mass spectrometer puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Real-time performance and the ability to access very large data arrays in main memory are key considerations. CSL evaluated alternatives to meet the data processing needs of the instrument and recommended a more recent model of the computer used for this purpose at Texas A&M University. This data system has been purchased and will be operational soon. Special interface electronics and stepping motor controllers for automatic tuning are under construction in CSL.

PL-00400
Rev. 1-6-81

Combined EDS-WDS X-ray Analysis Scanning Electron Microscope System

In 1979, following the recommendations of CSL, Dr. Hagins procured a combined energy dispersive (EDS) and wavelength-dispersive (WDS) X-ray analysis system for his scanning electron microscope. A single vendor did not market a combined EDS-WDS system. CSL arranged for the EDS vendor to integrate a WDS into their system. The system permits: localization and quantitation of both light and heavy elements in the sample, storage of raw and reduced data within the data system, processing of data, and transmission of data to a remote DECsystem-10 computer at DCRT. This system is complete and no further development is anticipated.

Cardiac Scintillation Probe

CSL has continued the development of its Cardiac Scintillation Probe System begun in 1977. This non-imaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. By simultaneously measuring LV volume and LV pressure, parameters such as LV compliance can be continuously monitored, in addition to such measurements as ejection fraction, filling and ejection rates, and temporal relationships. This year the previously implemented capability for realtime pressure-volume measurements were used to study the effects of naphidipine and verapamil on patients with asymmetric septal hypertrophy. The pressure-volume relationships produced by the probe system allowed the effects of drugs to be quantitated in a manner not possible before. New hardware and software have been developed to allow online calculation of new parameters and to permit the system to be easily used on a routine basis by the Clinical Center personnel. Development is continuing on increasing the detection efficiency of the probe and in quantifying the limitation of the technique.

PROJECT NUMBER Z01 CT00059-02 CSL	
FACILITY COVERED October 1, 1980 to September 30, 1981	
TITLE OF PROJECT (20 characters or less) Combined EDS-WDS X-ray Analysis Scanning Electron Microscope System	
NAME, LASTNAME AND FIRSTNAME, AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Ramon L. Tate, Ph.D. Computer Specialist CSL, DCRT OTHER: William A. Hagins, M.D., Ph.D. Chief, Membrane Biophysics Section LCP, NIADDK	
COOPERATING UNITS (if any) LCP, NIADDK	
LABORATORY Computer Systems Laboratory	
SECTION Processor Design Section	
INSTRUMENTS AND EQUIPMENT DCRT, NIH, Bethesda, MD 20205	
TOTAL PARTICLES 0.1 PROFESSIONAL 0.1 OTHER	
CHECK APPROPRIATE BOXES <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NUCLEAR	
CHECK (a) HUMAN SUBJECTS <input type="checkbox"/> (a) INTERVIEW	
SUMMARY OF WORK (200 words or less, or whatever necessary) In 1979, following the recommendations of CSL, Dr. Hagins procured a combined energy dispersive (EDS) and wavelength-dispersive (WDS) X-ray analysis system for his scanning electron microscope. A single vendor did not market a combined EDS-WDS system. CSL arranged for the EDS vendor to integrate a WDS into their system. The system permits: localization and quantitation of both light and heavy elements in the sample, storage of raw and reduced data within the data system, processing of data, and transmission of data to a remote DECsystem-10 computer at DCRT. This system is complete and no further development is anticipated.	
FINANCIAL (See 10-10)	

PROJECT NUMBER Z01 CT00051-02 CSL	
FACILITY COVERED October 1, 1980 to September 30, 1981	
TITLE OF PROJECT (20 characters or less) Cardiac Scintillation Probe	
NAME, LASTNAME AND FIRSTNAME, AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Harold Ostrow Electronics Engineer CSL, DCRT OTHER: Scott Allen Medical Research Analyst CSL, DCRT Steve Bacharach Physicist NM, CC Michael Green Physicist NM, CC Robert Benow Cardiologist CB, NHLBI Douglas Rosen Cardiologist CB, NHLBI	
COOPERATING UNITS (if any) Nuclear Medicine, CC, Cardiology Branch, NHLBI	
LABORATORY Computer Systems Laboratory	
SECTION Processor Design Section	
INSTRUMENTS AND EQUIPMENT DCRT, NIH, Bethesda, MD 20205	
TOTAL PARTICLES 1.0 PROFESSIONAL 1.0 OTHER	
CHECK APPROPRIATE BOXES <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NUCLEAR	
CHECK (a) HUMAN SUBJECTS <input type="checkbox"/> (a) INTERVIEW	
SUMMARY OF WORK (200 words or less, or whatever necessary) CSL has continued the development of its Cardiac Scintillation Probe System begun in 1977. This non-imaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. By simultaneously measuring LV volume and LV pressure, parameters such as LV compliance can be continuously monitored, in addition to such measurements as ejection fraction, filling and ejection rates, and temporal relationships. This year the previously implemented capability for realtime pressure-volume measurements were used to study the effects of naphidipine and verapamil on patients with asymmetric septal hypertrophy. The pressure-volume relationships produced by the probe system allowed the effects of drugs to be quantitated in a manner not possible before. New hardware and software have been developed to allow online calculation of new parameters and to permit the system to be easily used on a routine basis by the Clinical Center personnel. Development is continuing on increasing the detection efficiency of the probe and in quantifying the limitation of the technique.	
FINANCIAL (See 10-10)	

NATIONAL CENTER FOR HUMAN RESEARCH PROJECT NUMBER (SEE NHR 100-100-100)		DEPARTMENT OF HEALTH AND HUMAN SERVICES PROJECT TITLE (SEE NHR 100-100-100)		PROJECT NUMBER 201 CT00054-02 CSL	
PERIOD COVERED October 1, 1980 to September 30, 1981 TITLE OF PROJECT (See NHR 100-100-100)					
Medical Intensive Care Unit Patient Monitoring Computer System					
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLE OF PRINCIPAL INVESTIGATOR, AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI:	Kenneth M. Kemper	Electronics Engineer	CSL, DCRT		
	Robert L. Martino	Electronics Engineer	CSL, DCRT		
	Joseph E. Parrillo	Chief, Critical Care Medicine	CCMD, CC		
OTHER:	Arthur J. Pashayan	Computer Specialist	CSL, DCRT		
	Susan L. Huntley	Supv., Critical Care Technicians	CCMD, CC		
COOPERATING UNIT (S) (4 x 9)					
Critical Care Medicine Department, Clinical Center					
LABORATORY					
Computer Systems Laboratory					
SECTION					
Systems Design Section					
INSTITUTE AND LOCATION					
DCRT, N.H. Bethesda, MD 20205					
TITLE NUMBER					
0.5					
0.5					
DATA ACQUISITION METHOD					
<input checked="" type="checkbox"/> (4) HUMAN SUBJECTS <input type="checkbox"/> (2) HUMAN TISSUES <input type="checkbox"/> (2) VITRO					
<input type="checkbox"/> (4) MINDS <input type="checkbox"/> (2) INTERVIEW					
SUMMARY OF WORK (200 words or less - underline required)					
This project involves the development of an automated patient monitoring system for measurement, analysis, control, and record keeping functions in a nine bed medical intensive care unit. A minicomputer-based patient data management system, a cardiovascular research subsystem, a software development subsystem, and a medical mass spectrometer subsystem are already operational. Future project goals involve the development of noninvasive measurements of the cardiovascular and respiratory system, computer-controlled drug infusion, and automated urine output measurement. A data base of the patient information obtained with the systems will be created and used for retrospective studies by the medical staff.					
PROJECT (NHR 100-100-100)					

Medical Intensive Care Unit Patient Monitoring Computer System

This project involves the development of an automated patient monitoring system for measurement, analysis, control, and recordkeeping functions in a nine-bed medical intensive care unit. A minicomputer-based patient data management system, a cardiovascular research subsystem, a software development subsystem, and a medical mass spectrometer subsystem are already operational. Future project goals involve the development of noninvasive measurements of the cardiovascular and respiratory systems, computer-controlled drug infusion, and automated urine output measurement. A data base of the patient information obtained with the systems will be created and used for retrospective studies by the medical staff.

Background and Objectives: The Medical Intensive Care Unit (MICU), which is administered by the Department of Critical Care Medicine in the NIH Clinical Center, receives critically ill patients from clinical programs of NIH. The MICU comprises a five-bed ward area, a two-bed special study area, a pair of isolation beds, and a vascular research laboratory. The research goals of this unit include the development of techniques for automated patient monitoring and noninvasive measurements of the cardiovascular and respiratory systems. In addition, the medical staff is performing complete cardiac catheterization studies.

Over the past four years, CSL has invested six man-years in this project. Working with clinical center staff, CSL contributed to the engineering design of the intensive care unit. CSL also undertook the specification, procurement, and installation of the bedside patient monitoring equipment and four computer systems:

1. a Patient Data Management System used for automatically monitoring patient variables, manually entering patient data, retrieving information online, and keeping medical records;
2. a Cardiovascular Research Subsystem used for acquiring and processing cardiovascular pressure waveforms, measuring cardiac output, displaying measured results online, and generating a cardiac catheterization report;
3. a Software Development Subsystem used for developing software for the above described systems; and
4. a Medical Mass Spectrometer Subsystem used for monitoring both the patient airway gases and the gases delivered by the patient's respirator at all nine beds. Featuring the same minicomputer, the first

three systems were purchased from the Hewlett-Packard Corporation. The Chemetron Corporation manufactures the microprocessor-based mass spectrometer system.

Major Findings: The automation of the MICU has aided the medical staff by: managing the large amount of data needed for the care of the critically ill patient, performing desired calculations, and allowing measurements that would not otherwise be possible.

Progress in FY81: The four computer systems have been in operation for over two years. The departure of the unit's senior staff at the end of the last reporting year resulted in the temporary cessation of hardware/software development. With the arrival of a new department chief, a reconsideration of system goals was undertaken. Particular emphasis was placed on upgrading the system's cardiac catheterization capabilities. Data collection and retrieval functions of the primary patient data management system are being reconfigured to support anticipated research protocols.

Significance to Biomedical Research: Many hospitals around the world are automating various functions in their intensive care units. In particular, the Hewlett-Packard computerized patient monitoring system purchased for this project has been installed in many private, university, and government hospitals. Therefore, any new developments made on this project will benefit many users of automated systems, as well as patient care and clinical research within the MICU at NIH.

Proposed Course: Depending on the research goals of the new medical staff, possible modifications to the primary patient data management system include the addition of urine output measurement hardware and the computerization of fluid infusion therapy with microprocessor-controlled infusion pumps. In addition, software modifications to the patient data management and vascular research computers can tailor their functional capabilities to the unit's developing research interests.

Publications:

Martino, R. L., Kempner, K. M., McClellan, J. R., and McLees, B. C.: Automation of a Medical Intensive Care Environment with a Flexible Configuration of Computer Systems. *Proceedings of the Fourth Annual Symposium on Computer Applications in Medical Care*. New York, Institute of Electrical and Electronics Engineers, Inc., 1980, pp. 1562-1658.

SPONSORING/SCIENCE/TECHNOLOGY/TECHNICAL PROJECT NUMBER (DD FORM 104-104-104)	U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE NATIONAL INSTITUTE OF HEALTH BIOMEDICAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00053-02 CSL
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (Do not exceed 100 words) Cardiac Intensive Care Unit Patient Monitoring Computer System		
PRINCIPAL INVESTIGATOR AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER		
PI: Kenneth M. Kempner, Electronics Engineer, CSL, DORT Andrew G. Morrow, M.D., Chief, SB, NHLBI Charles L. McCleskey, M.D., Senior Surgeon		
OTHER: William L. Rizzo, Electronics Engineer, CSL, DORT Robert L. Martino, Electronics Engineer, CSL, DORT Lee Freeman, Computer Programmer, CSL, DORT		
CONTROLLING UNIT (If any) Surgery Branch, NHLBI		
DEVELOPER Computer Systems Laboratory		
SYSTEMS DESIGN SECTION PREPARED BY: DORT, HRP, Bethesda, MD, 20205		
TOTAL PERSONNEL 0.5 PERCENTAGE 0.5 OTHER:		
SELECT AUTOMATED MODES:		
<input type="checkbox"/> (a) HUMAN INTERFACES <input type="checkbox"/> (b) HUMAN PHYSICS <input type="checkbox"/> (c) NEUTRON		
<input type="checkbox"/> (d) WAVEFORMS <input type="checkbox"/> (e) INTERFACES		
ABSTRACT OF WORK (200 words or less - abstracts required) The computerized patient monitoring system developed in conjunction with Surgery Branch, NHLBI, provides real-time, beat-to-beat analysis of physiologic waveforms from patients within a four-bed intensive care unit. Based around a Xerox Sigma-3 Computer, the system monitors the electrocardiogram, arterial and venous blood pressures, body temperature, urine output, and blood loss, as well as thermal and oxygenation cardiac output. A Morphology Analysis of the electrocardiogram and arterial blood pressure waveforms is performed to detect fiducial markers. The application of cross-correlation techniques to the electrocardiogram allows the detection of premature ventricular contractions. Beat-to-beat data from the most recent thousand electrocardiographic complexes may be recalled at any time in the form of Joint Interval Histograms and Correlation Coefficient Scatter Diagrams. A five-minute electrocardiogram memory is maintained in real-time for use in the detection of transient ventricular arrhythmias. Vital signs are retrievable as eight-hour nursing shift summaries in tabular form, or as 12-, 24-, or 72-hour vital signs graphs.		
PD-4400 (Rev. 10-79)		

Cardiac Intensive Care Unit Patient Monitoring Computer System

The computerized patient monitoring system developed in conjunction with Surgery Branch, NHLBI, provides realtime, beat-to-beat analysis of physiologic waveforms from patients within a four-bed intensive care unit. Based around a Xerox Sigma-3 Computer, the system monitors the electrocardiogram, arterial and venous blood pressures, body temperature, urine output, and blood loss, as well as thermal and dye-dilution cardiac output.

A Morphology Analysis of the electrocardiogram and arterial blood pressure waveforms is performed to detect fiducial markers. The application of cross-correlation techniques to the electrocardiogram allows the detection of premature ventricular contractions. Beat-to-beat data from the most recent thousand electrocardiographic complexes may be recalled at any time in the form of Joint Interval Histograms and Correlation Coefficient Scatter Diagrams. A five-minute electrocardiogram memory is maintained in realtime for use in the detection of transient ventricular arrhythmias. Vital signs are retrievable as eight-hour nursing shift summaries in tabular form, or as 12-, 24-, or 72-hour vital signs graphs.

Background and Objectives: The principle objective of this long-term project was to investigate new approaches to the problem of providing an automated patient monitoring environment. More specifically, project goals include: the release of the nursing staff from routine clerical tasks, the uniform collection of all vital signs at high frequency, the automated detection of potentially life-threatening ventricular arrhythmias, and the development of an online tool for the evaluation of signal processing algorithms.

Methods Employed: A general-purpose process-control computer system was chosen as the central element of the interactive patient monitoring system. The Xerox Sigma-3 computer was interfaced to a high-speed 16-channel video generator system. Commercially available bedside electronic modules were chosen to provide for the monitoring of all relevant physiologic parameters. Transducers were developed to monitor urine output and blood loss (chest drainage). Active analog and digital transmission lines were fabricated to connect the intensive care unit with the computer room.

The operating system provided with the Xerox Sigma-3 was extensively modified to provide a more suitable environment for realtime, beat-to-beat

patient monitoring tasks. Many signal analysis programs, and a sophisticated graphics package, were written to accomplish the functional specifications selected for this system.

Major Findings in FY81: No major findings occurred during FY81. The system was maintained in continuous operation without additional hardware/software development or evaluation. The use of this system was terminated at the end of December in anticipation of the relocation of the Surgery Branch to new facilities within the Clinical Center. This system had been in place for ten years, but because the mainframe hardware was no longer in production, replacement parts and maintenance became an increasing burden. Design of the new five-bed intensive care unit was carefully planned to incorporate all utilities, conduits, and structural accommodations necessary for the computerization of the unit.

Significance to Biomedical Research: The computerized patient monitoring system can be practically applied to the continuous collection of data for research protocols.

The novel approach to the monitoring of cardiac arrhythmias implemented on this system is easily adaptable to other computer systems with waveform capture capability. These arrhythmia monitoring techniques should prove useful in many clinical and experimental animal protocols, such as drug evaluation studies.

Proposed Course: A final decision must be reached concerning the desired approach for replacement of the previously developed ICU Monitoring Computer System. Some factors to be considered are: medical utility of computerization, trade-offs of alternative systems, time for implementation, staffing for design/implementation, and operational personnel required. The selected approach would then be carried through the final design phase, including a detailed cost estimate.

INSTITUTION (GENERAL INFORMATION) LABORATORY PROJECT NUMBER (DO NOT USE THIS SPACE)		U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE NCI INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00052-02 CSL
PERIOD COVERED October 1, 1980 to September 30, 1981			
TITLE OF PROJECT (DO NOT EXCEED 100 CHARACTERS)			
Computerized Radiation Therapy			
NAMES, LABORATORY AND INSTITUTION ABBREVIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
PI:	H. Fredrickson J. Van de Geijn	Computer Systems Analyst Chief, Radiation Physics & Computer Automation Section	CSL, ORCT ROB, DCT, NCI
OTHER:	N. Rizzo D. Syed E. Glustein	Electronics Engineer Chief, Systems Design Section Chief, Radiation Oncology Branch	CSL, ORCT CSL, ORCT ROB, DCT, NCI
COOPERATING UNITS (If any)			
Radiation Oncology Branch, NCI			
LABORATORY Computer Systems Laboratory			
SECTION Systems Design Section			
INSTITUTION AND LOCATION ORCT, NCI, Bethesda, MD 20205			
TOTAL MANPOWER: PROFESSIONALS: 1.0 OTHER: 1.0			
OTHER APPROPRIATE DATA(S): <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEITHER			
<input checked="" type="checkbox"/> (a) MINDS <input type="checkbox"/> (b) INTERVIEWS SUMMARY OF WORK (200 CHARACTERS OR LESS - UNLESS OTHERWISE SPECIFIED)			
CSL has developed a computer system, now in clinical operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from computer assisted tomography to improve radiation treatment planning. This system for external beam treatment planning is based on a generalized 3-D dose field model that covers photon, electron, and neutron beams.			
The computer program and most of its clinical implementation has been completed for the photon and electron fields available from the local 6 MV and 12 MV linear accelerators. The current capabilities include interactive simulation of most irradiation techniques, including the effect of most beam modifying devices. The system enables the display of dose distributions computed in several transverse contours and overlaid on corresponding CT scans.			
PRINCIPAL INVESTIGATOR (Name, Title)			

Computerized Radiation Therapy

CSL has developed a computer system, now in clinical operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from computer assisted tomography to improve radiation treatment planning. This system for external beam treatment planning is based on a generalized 3-D dose field model that covers photon, electron, and neutron beams.

The computer program and most of its clinical implementation has been completed for the photon and electron fields available from the local 6 MV and 12 MV linear accelerators. The current capabilities include interactive simulation of most irradiation techniques, including the effect of most beam modifying devices. The system enables the display of dose distributions computed in several transverse contours and overlaid on corresponding CT scans.

Background and Objectives: During the past five years, CSL has maintained an active collaborative relationship with staff of the Radiation Oncology Branch, NCI. The goal of this effort is to develop and implement a generalized system for computer assisted radiation treatment planning. Initially aimed at utilizing CT scans during planning, the scope of the project has now broadened.

Methods Employed: The dose field model developed by Jan van de Geijn was implemented in RSX-11M FORTRAN and experimentally tested for the local radiation facilities. The theoretical model was extended to cover irregularly-shaped beams as well as irregularly-shaped shielding blocks. Emphasis has been placed on optimization of interactive operational facilities and accommodations of input and hard copy techniques to clinical demands.

Major Findings: The system is now in routine use for clinical treatment planning. It offers high speed computation and display of complete dose distributions in multiple slices, superimposed on CT images, including effects of wedge filters, shielding blocks, and diaphragm rotation.

Significance to Biomedical Research: The convenient interactive manipulation of key beam parameters in combination with fast response is highly valuable in complicated dosimetry problems encountered in special protocol studies.

Proposed Course:

- Implement the Dose Field Model for regular and irregular electron fields.
- Establish multiple treatment planning stations to allow simultaneous use of the computer display equipment.

- Extend the capabilities to compute and display dose distributions in sagittal and coronal sections of the patient.

Publications:

Padikal, T., Lichter, A., Tepper, J., Glatstein, E., Schwade, J., Fredrickson, H., Rizzo, W., Roberson, P., Iler, V., Van de Geijn, J., and Kinsella, T.. Experience with a CT Based Treatment Planning System. In O'Neill, J. T. (Ed.): *Proceedings of the Fourth Annual Symposium on Computer Applications in Medical Care*. New York, Institute of Electrical and Electronics Engineers, 1980, pp. 83-88.

Image Processing Facility

This project is intended to provide a utility to display and analyze digital images. The system will consist of a powerful 32-bit computer with a mixture of medium- and high-resolution video displays. Also, the system will include a microdensitometer to allow precise digitization of x-rays, micrographs and other images. The computer and peripherals have been purchased, with delivery expected during the next fiscal year, and the design for physical space to house the system is complete. Construction will begin soon, with completion expected during the next eight months. The display subsystem specifications are complete, and procurement is expected during the next year.

Background and Objectives: This project arose in response to a critically overcrowded situation that exists on the present DCRT Evans and Sutherland Graphics computer. As image processing applications at NIH have increased, the limited resources of that graphics system have been saturated. During FY80, CSL, in collaboration with present and potential users designed a new general-purpose computer facility to aid the acquisition, display, and analysis of images such as electron micrographs, CAT scans, and radiographs. This facility will be available for use by the NIH community.

Progress in FY81: The system will be based on a 32-bit, one megabyte computer, with a smaller 16-bit processor to handle image acquisition. A multidisplay raster scan frame buffer will provide several users concurrent access to the central processor. Images will be digitized when necessary through a microdensitometer or a vidicon camera. Hard copy will be provided by a camera system.

The computers and several related peripherals have been purchased, with delivery expected toward the middle of next year. A formal 'Request for Proposals' for the display sub-systems has been prepared and is awaiting funding for purchase next year. The design for the physical space of this facility is complete, and a contract for the construction should

be awarded early in FY82.

Significance to Biomedical Research: Study of images obtained in the biomedical laboratory is proving more and more fruitful as technology is able to supply the proper tools at a reasonable cost. Biomedical scientists are employing image analysis for a wide variety of research goals, and the use of such techniques is expected to grow very rapidly in the near future.

Proposed Course: Pending the availability of funds, the outstanding system components will be purchased, the physical site will be prepared, and the development work to assemble the various parts into a working system will begin.

PERIOD COVERED October 1, 1980 to September 30, 1981 TITLE OF PROJECT (50 characters or less) Digital Imaging Applications in Cardiovascular Research		PROJECT NUMBER Z01 CT00073-02 CSL	
NAME, ADDRESS AND TELEPHONE, MAILING ADDRESS, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONNEL PERSONNEL ENGAGED ON THE PROJECT PI: Douglas Foxvog Computer Specialist CSL, DCRT Michael Jones Senior Surgeon H 1R 50, NHLBI OTHER: William Barrett Staff Fellow CSL, DCRT James M. Deleo Computer Systems Analyst CSL, DCRT Benes Trus Research Chemist CSL, DCRT Joseph Zischenberger Clinical Associate H 1R 50, NHLBI			
COOPERATING AGENCY (if any) Clinic of Surgery, NHLBI			
LABORATORY Computer Systems Laboratory			
SECTION Systems Design Section			
FACILITY AND LOCATION DCRT, NIH, Bethesda, MD 20205			
TOTAL MANPOWER 3.2 PROFESSIONAL 1.2 OTHER			
DATA APPROPRIATE REUSE(S) <input checked="" type="checkbox"/> (1) PRIMARY SUBJECTS <input type="checkbox"/> (2) HUMAN TISSUES <input checked="" type="checkbox"/> (3) MATERIAL			
(1) (2) (3) (4) (5) (6) (7) (8) (9) (10) (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78) (79) (80) (81) (82) (83) (84) (85) (86) (87) (88) (89) (90) (91) (92) (93) (94) (95) (96) (97) (98) (99) (100)			
SUMMARY OF WORK (500 words or less - underline headings) Digital image analysis has been applied to several topics in myocardial and valvular research. This project has been renamed from last year to reflect a somewhat broader scope. •Morphometric analysis of myocardial hypertrophy. Software has been developed to enable interactive analysis of samples of hypertrophied myocardium from humans and from experimental animals. These packages allow determination of cell diameter, nuclei densities, capillary densities, and percent interstitium. •Bioprosthetic heart valve studies. To investigate the cause of stenosis of bioprosthetic valves, diseased valves are removed from experimental animals and imaged radiographically, and after sectioning, by photography. Analysis can quantify sites of calcification, and the amounts of fibrous sheath and normal tissue. •Regional myocardial blood flow. Quantitative data from experimental animals are displayed as a map of the heart, with increases in blood flow indicated by variations in intensity or color. Comparison of epicardial-endocardial flows and control vs. test data will be studied.			

PERIOD COVERED October 1, 1980 to September 30, 1981 TITLE OF PROJECT (50 characters or less) Cerebral Metabolic Imaging		PROJECT NUMBER Z01 CT00073-02 CSL	
NAME, ADDRESS AND TELEPHONE, MAILING ADDRESS, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONNEL PERSONNEL ENGAGED ON THE PROJECT PI: Douglas Foxvog Computer Specialist CSL, DCRT James M. Deleo Computer Systems Laboratory CSL, DCRT Louis Solovoff Chief LCM, NIMH Charles F. Goochee Computer Programmer LCM, NIMH			
COOPERATING AGENCY (if any) Laboratory of Cerebral Metabolism (LCM), NIMH			
LABORATORY Computer Systems Laboratory			
SECTION Systems Design Section			
FACILITY AND LOCATION DCRT, NIH, Bethesda, Maryland 20205			
TOTAL MANPOWER 0.1 PROFESSIONAL 0.1 OTHER			
DATA APPROPRIATE REUSE(S) <input type="checkbox"/> (1) PRIMARY SUBJECTS <input type="checkbox"/> (2) HUMAN TISSUES <input checked="" type="checkbox"/> (3) MATERIAL			
(1) (2) (3) (4) (5) (6) (7) (8) (9) (10) (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78) (79) (80) (81) (82) (83) (84) (85) (86) (87) (88) (89) (90) (91) (92) (93) (94) (95) (96) (97) (98) (99) (100)			
SUMMARY OF WORK (500 words or less - underline headings) An algorithm to align spatially sequential, parallel images of autoradiographs showing cerebral metabolic activity in microtomed sliced sections of experimental animal brains has been developed to facilitate arbitrary plane viewing in the three-dimensional image space resulting from the stacking of aligned parallel images. Use of the algorithm, which is based on minimizing non-overlapping areas, demonstrates the need for fixed fiducial reference points in specimen images. Preliminary attempts in preparing specimens to provide fiducial points illustrate the difficulty of this task. LCM will continue algorithm development on the newly installed NIMH De Anza Imaging System. LCM will remain available for consultation.			

Digital Imaging Applications in Cardiovascular Research

Digital image analysis has been applied to several topics in myocardial and valvular research. This project has been renamed from last year to reflect a somewhat broader scope.

- Morphometric analysis of myocardial hypertrophy. Software has been developed to enable interactive analysis of samples of hypertrophied myocardium from humans and from experimental animals. These packages allow determination of cell diameter, nuclei densities, capillary densities, and percent interstitium.
- Bioprosthetic heart valve studies. To investigate the cause of stenosis of prosthetic valves, diseased valves are removed from experimental animals and imaged radiographically, and after sectioning, by photography. Analysis can quantify sites of calcifications and the amounts of fibrous sheath and normal tissue.
- Regional myocardial blood flow. Quantitative data from experimental animals are displayed as a map of the heart, with increases in blood flow indicated by variations in intensity or color. Comparison of epicardial-endocardial flows and control vs. test data will be studied.

Background and Objectives: This project applies computer assisted digital imaging techniques to areas of interest in cardiovascular research. The project began last year with the morphological analysis of cardiac tissue, and this year includes a preliminary study of bioprosthetic heart valves and development of a system to examine regional myocardial blood flow.

Methods Employed:

- Morphometric Analysis. Specimens are microtomed, mounted, stained, and photographed under a light microscope. Resultant negatives are then digitized by microdensitometry, and entered into the Evans and Sutherland display computer. The programs calculate myocyte cross-sectional areas, myocyte diameter and perimeter, capillary and nuclei count, and statistics on one or more than one sample.
- Bioprosthetic heart valves. Transverse microtome sections taken from the valve leaflets and radiographs of the valve are scanned for computer input. The amount of calcification, fibrous sheath, and normal leaflet tissue can be determined quickly and efficiently using an interactive contouring and thresholding algorithm.

- **Regional blood flow.** Data are obtained from the injection and tracking of tagged microspheres. The epicardial and endocardial wall of the right and left ventricle as well as both sides of the septal wall are examined. Numerical data consisting of regional blood flow measurements are represented graphically as varying shades of intensity or color. Values between adjacent regions can be interpolated to form a more continuous surface, with high to low flow variations represented by a rainbow color spectrum. This should provide an effective means for the visualization of flow patterns in a single animal and of the distribution of flow patterns over the entire experimental population.

Progress in FY81: An interactive computer program MORPH has been used to study the left ventricular mid-anterior wall of adult foxhounds as part of a preliminary study of the effectiveness, accuracy, and utility of computer-assisted morphometric analysis. In addition to inherent reproducibility, the variance per sample analyzed decreases tenfold when compared to manual point counting techniques. There is also a ten percent reduction in the standard error of the estimate for the mean interstitial fraction of a tissue evaluated from five separate microscope fields. The primary benefit of this method is in facilitating the analysis of multiple fields and multiple slides per tissue sample. Increasing the number of samples decreases the overall variance proportionally. Programs that display regional blood flow and provide ratio comparisons of endocardial and epicardial flow have been completed.

Significance to Biomedical Research: These digital image analysis techniques provide scientists with accurate, reproducible, and efficient tools, superseding alternate manual approaches such as planimetry or point counting.

Proposed Course: This project will continue to refine the morphometric analysis now in use, and extend the techniques to three-dimensional examination of cardiac muscle cells by reconstruction from thin slices of human and animal cells. The prosthetic valve study will resume after leaflets are resectioned, to produce a more anatomically consistent data base than was previously obtained. Regional blood flow studies will continue. Methods are to be devised to meaningfully compare myocardial blood flow during different tests on one animal, as well as to compare different animals. Correlation of endocardial with epicardial flows will also be provided.

Cerebral Metabolic Imaging

An algorithm to align spatially sequential, parallel images of autoradiographs showing cerebral metabolic activity in microtomed sliced sections of experimental animal brains has been developed to facilitate arbitrary plane viewing in the three-dimensional image space resulting from the stacking of aligned parallel images. Use of the algorithm, which is based on minimizing non-overlapping areas, demonstrates the need for fixed fiducial reference points in specimen images. Preliminary attempts in preparing specimens to provide fiducial points illustrate the difficulty of this task. LCM will continue algorithm development on the newly installed NIMH DeAnza Imaging System. CSL will remain available for consultation.

Background and Objectives: The Laboratory of Cerebral Metabolism, NIMH has been engaged in computer-assisted image processing of autoradiographs that illustrate cerebral metabolic activity in microtome-sliced sections of experimental animal brains since 1977. In 1979, the Computer Systems Laboratory was asked to collaborate in the development of a methodology to enhance and align spatially sequential microtome brain slice images for the purpose of reconstructing alternate views through this three-dimensional image data. Algorithms developed by CSL on the DCRT Evans and Sutherland Image Processing System were to be transportable to a DeAnza image processing system on order by NIMH.

Methods Employed: CSL has implemented software to align sequential images by an algorithm which minimizes overlapping areas. The limitations of this approach are especially evident when aligning images in which brain segments are physically detached. It was, therefore, agreed to investigate new methods of specimen preparation that would provide fixed fiducial marker points to enhance automated alignment.

Major Findings: To assure quality three-dimensional imaging of cerebral metabolic activity, it is essential to have sufficient internal and/or external fixed fiducial marker points to facilitate automated alignment. Unsuccessful early attempts in specimen preparation to provide fiducial points illustrate the complexity of this problem.

Proposed Course: Procedures and algorithms developed by CSL have been given to LCM. Now that the new NIMH DeAnza image processing system has arrived, LCM staff members will continue algorithm development on that system. CSL staff will continue to be available for consultation in this work.

This project, which was transferred from NIDR during this reporting period, is intended to design hardware and software mechanisms for the computer analysis of one- and two-dimensional gel electrophoresis. Image processing is being used to evaluate and compare differences in protein composition. Only computer analysis can make such comparisons strictly quantitative. Analysis of two-dimensional gels is completely automatic, while analysis of one-dimensional gels is interactive. Additional applications with autoradiographs are being investigated.

Significance to Biomedical Research: Use of gel electrophoresis or autoradiographs is commonplace in chemical, biochemical, and biomedical analysis. However, the quantization or comparison of such gels is tedious, qualitative, and difficult. Use of the Evans and Sutherland system to evaluate such samples permits scientists greater information with increased reliability and simplicity of operation.

Methods Employed: Samples are scanned on the Perkin-Elmer microdensitometer and stored on magnetic tape for later processing. Two-dimensional gels are processed by a program, CINT (Computer Integration), which corrects for background, automatically locates peaks, automatically integrates all peaks, and provides a printed summary of results. In addition, an image can be obtained either from the video frame buffer or from a Calcomp plotter. Two or more gels can be compared graphically by means of a program OVERLP which correlates two gels and provides data to generate overlapping Calcomp plots.

with each gel as a different color.

Proposed Course: Computer software will be expanded to encompass new types of data. A prime consideration of software development has been machine independence, and the software can thus be easily transported to other private facilities. With the acquisition of the image processing laboratory hardware, the present programs will be converted to execute more quickly and efficiently.

Publications:

Nikodem, V. M., Trus, B. L., and Rall, J. E.: Two-Dimensional Gel Analysis of Rat Liver Nuclear Proteins after Thyroidectomy and Thyroid Hormone Treatment. *Proceedings of the National Academy of Sciences* (in press).

Automated Analysis of Plaque Formation in Experimental Atherosclerosis

Computer programs have been developed and packaged for detecting and quantitating atherosclerotic disease formation and its location along the entire arterial tree, and for statistical correlation of disease patterns with anatomy, diet, and vessel wall permeability. Permeability is indicated with Evans' Blue dye and disease is indicated with Sudan IV Red dye. Colors are separated using appropriate filters in the scanning process and the resulting digital images are transformed to a standard coordinate system. An iterative edge-finding algorithm searches the image for an optimal threshold of maximum optical intensity to identify and isolate diseased areas. Topographic maps, formed by overlaying the disease patterns from different animals, show the incidence and coincidence of disease at a given location. The maps describe the extremely congruent distribution of the disease in a concise and quantitative manner and provide the researcher with a tool for correlation of disease patterns with local histologic, physical, and biomedical events.

Background and Objectives: Atherosclerosis was produced experimentally in 41 animals by feeding them high-calorie, cholesterol-rich diets. Eleven control animals were also included in the population for comparison with the experimental group. Prior to sacrifice, animals were injected with Evans' Blue dye, an indicator of vessel wall permeability. A systematized necropsy procedure and standardized format were developed for arranging and fastening the opened arterial tree to reflective panels, after which the vessel segments were stained with Sudan IV Red dye to indicate areas of disease.

Although atherosclerosis is a multifaceted disease, experimental studies indicate that this disease is very discrete and local in occurrence. Moreover, the patterns of distribution of sudanophilic lesions tend

to have a characteristic common topography in a given species. Thus, it is important to define the spatial occurrence statistically to facilitate correlation of disease patterns with local structural, chemical, histological, and fluid mechanical events.

Methods Employed: Thirty-five millimeter slides of the preparations are scanned at a resolution of 50 microns using neutral density, red, and blue filters. Digitized images are displayed and analyzed on an Evans and Sutherland Video Frame Buffer. Images are transformed to a common coordinate system through the use of local anatomical landmarks, the coordinates of which are identified by a technician familiar with the anatomy, using a graph pen and a tablet that is interfaced to the computer (PDP-11/70) driving the display. An iterative edge-finding algorithm outlines the image at an initial intensity value, and then performs an orthogonal search of the outlines to identify an optimal threshold, which is used to segment the image into areas of disease and non-disease.

Thresholded images corresponding to a given arterial segment are added together to produce a topographic map representing the location and relative frequency (probability) of lesion occurrence in a given population of animals. The map is displayed on a video screen by using various intensity values or colors to represent levels of incidence and coincidence of the disease. The intersection of two different maps provides a quantitative measure of the correlation between disease patterns as they occur in different groups of animals, or between different variables within the same group.

Major Findings: Programs for image processing and analysis, file management, storage, retrieval, and review of results, have all been efficiently integrated into a system. Close to 1000 images have now been processed, producing topographic maps showing the statistical distribution of the disease along major arterial pathways. The eight hours previously required to manually identify landmarks and transform images has been reduced to approximately three minutes, making this objective and statistical approach practical. In addition, automated thresholding of disease patterns compares favorably with manual methods, while reducing the time involved and assuring reproducibility.

The probability maps illustrate the consistent distribution of disease patterns and show a strong relationship between these patterns and the anatomical detail in the vessel wall. This is striking

AUTH. (LAB. CTR.) (CLIN. CENTER) (ADMIN. PROJECT NUMBER) (SEE 201 AND 202A) (SEE 202A)		JUL. DEPARTMENT OF HEALTH AND HUMAN SERVICES NATIONAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00074-02 CSL
PERIOD COVERED October 1, 1980 to September 30, 1981				
TITLE OF PROJECT (IN CHARACTERS OF LINE) Computerized Three-Dimensional Model of the Cat's Brain Stem				
NAME, LABORATORY AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Douglas A. Fowsey Computer Specialist CSL, DCRT James M. DeLeo Computer Systems Analyst CSL, DCRT Joe Adams Senior Staff Fellow LND, NINDS				
COOPERATING UNITS (IN WY) Laboratory of Neuro-otology, LND, NINDS				
LABORATORY Computer Systems Laboratory SECTION Systems Design Section				
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205				
TOTAL MANPOWER 0.2		PROFESSIONAL 0.2		STAFF 0.2
CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NEURON				
<input type="checkbox"/> (a) MIND <input type="checkbox"/> (a) INTERVIEW SUMMARY OF WORK (200 words or less - submitters required) A three-dimensional, colored, 60° volume element block model representing the neuronal structure of the superior olivary complex of a cat's brain stem has been developed. The model allows rapid selection of a viewing surface computed for any selected cutting plane through the model volume. The model provides a common frame of reference for comparing anatomical and physiological data from different experimental animals. Investigators should be able to view a section of the "normal" cat on the same plane as the experimental sections and also along the plane described by various electrode penetrations in the experimental animal. The model has been developed and used successfully on the Evans and Sutherland System. Publication-quality output has been produced. An atlas of over 150 views is being submitted to a medical journal.				
PI-60488 (Rev. 2-81)				

AUTH. (LAB. CTR.) (CLIN. CENTER) (ADMIN. PROJECT NUMBER) (SEE 201 AND 202A) (SEE 202A)		JUL. DEPARTMENT OF HEALTH AND HUMAN SERVICES NATIONAL RESEARCH PROJECT		PROJECT NUMBER 201 CT 00081-01 CSL
PERIOD COVERED October 1, 1980 to September 30, 1981				
TITLE OF PROJECT (IN CHARACTERS OF LINE) Rehabilitation Medicine Department Computer System				
NAME, LABORATORY AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: R. L. Martino Electronics Engineer CSL, DCRT M. Schneiderman Chief, Physical Therapy Service RA, CC R. L. Gertner Chief, Rehabilitation Medicine Dept. RA, CC				
COOPERATING UNITS (IN WY) Rehabilitation Medicine Department, Clinical Center				
LABORATORY Computer Systems Laboratory SECTION Systems Design Section				
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205				
TOTAL MANPOWER 0.4		PROFESSIONAL 0.4		STAFF 0.4
CHECK APPROPRIATE BOXES: <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEURON				
<input type="checkbox"/> (a) MIND <input type="checkbox"/> (a) INTERVIEW SUMMARY OF WORK (200 words or less - submitters required) This project involves the development of computer techniques in rehabilitation medicine in collaboration with the Rehabilitation Medicine Department of the NIH Clinical Center. The CSL has recommended computer techniques that can be used to automatically acquire anatomical and physiological information from patients, perform the required calculations on the data obtained, and display the necessary results to the medical staff. The automated techniques include the measurement of body forces (hand and ground reaction forces), muscle activity (monitoring the electromyogram muscles), and body kinetics (the position and angles of the limbs and joints in space and time). The system will also allow the medical staff to easily enter patient and staff data into a data base with computer generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data. In FY82 the CSL will continue the work begun in FY81 including the specification of the computer system, the evaluation of methods to perform the desired measurements, the selection of the necessary transducers and instrumentation, and the specification of the required software.				
PI-60488 (Rev. 10-81)				

evidence that the formation of lesions is strongly influenced by local factors such as hemodynamic forces acting on the surrounding anatomy. Areas of coincidence or 'hot spots' indicated a high statistical occurrence of sudanophilic lesions and may point to key locations in the genesis of the disease. Maps have also been created as a function of diet, and show a dramatic difference in the propagation of disease patterns when factors such as cholesterol and thyroid inhibitor are added to the diet. Preliminary results show a high correlation ($r=.92$) between maps created from the red and blue stained images, indicating a striking relationship between sites of lesion formation and vessel wall permeability. However, this relationship appears to be most pronounced near the periphery of a lesion when studied on an individual basis.

Proposed Course: The present study will culminate with the processing of the coronary arteries, a site of vital clinical interest. Correlation between Evans' Blue and Sudan IV images will be completed in an effort to further quantitate the relation between vessel wall permeability and disease. It is hoped that results of this study will not only help to characterize the pattern and distribution of atheromatous plaque formation, but will provide the researcher with a tool for further investigation into the cause and mechanism of the disease.

Publications:

Barrett, W. A., DeLeo, J. M., Cornhill, J. F., and Fry, D. L.: A system for Automated Analysis of Plaque Formation in Experimental Atherosclerosis. *53rd Scientific Sessions of the American Heart Association*, November 19, 1980.
Barrett, W. A.: An Iterative Algorithm for Multiple Threshold Detection. *IEEE Conference on Pattern Recognition and Image Processing*, August, 1981.

Computerized Three-dimensional Model of the Cat's Brain Stem

A three-dimensional, colored, volume element (60-cubed) block model representing the neuronal structure of the superior olivary complex of a cat's brain stem has been developed. The model allows rapid selection of a viewing surface computed for any selected cutting plane through the model volume. The model provides a common frame of reference for comparing anatomical and physiological data from different experimental animals. Investigators should be able to view a section of the 'normal' cat on the same plane described by various electrode penetrations in the experimental animal. The model has been developed and used successfully on the Evans and Sutherland System. Publication-quality output has been produced. An atlas of over 150 views is being submitted for publication.

Background and Objectives: The objectives of this project were:

1. To develop and implement a three-dimensional block model of a cat's brain stem for laboratory-collected data specifying cell types and their spatial relationships.

2. To provide a method for producing publication-quality colored and black-and-white two-dimensional graphics that illustrate the three-dimensional graphics block model.

Methods Employed: Consecutive 80-micron-thick microtomed slices for the superior olivary complex of the cat's brain stem were stained and examined by a neuroanatomist by means of a Zeiss microscope. The stage of the microscope was attached to a computer, as was a function box, thus enabling the neuroanatomist to log spatial coordinates and cell types in a computer data file. This data was transferred to the Evans and Sutherland System and used as input to the volume element (60-cubed) block model program specifically developed for this project. The block model software allows the investigator to view the surface of any selected cutting plane through the model volume.

Progress in FY81 Publication-quality output has been produced. The software developed for this project has shown itself to be applicable to several other biomedical imaging applications.

Proposed Course: This project has been completed. It is expected that the block model software will be extended to other applications.

Rehabilitation Medicine Department Computer System

This project involves the development of computer techniques in rehabilitation medicine in collaboration with the Rehabilitation Medicine Department of the NIH Clinical Center. CSL has recommended computer techniques that can be used to automatically acquire anatomical and physiological information from patients, perform the required calculations on the data obtained, and display the necessary results to the medical staff. The automated techniques include: the measurement of body forces (hand and ground reaction forces), muscle activity (monitoring the electromyogram of muscles), and body kinematics (the position and angles of the limbs and joints in space and time). The system will allow the medical staff to easily enter patient and staff data into a data base with computer-generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data. In FY82 CSL will

continue the work begun in FY81 including the specification of the computer system, the evaluation of methods to perform the desired measurements, the selection of the necessary transducers and instrumentation, and the specification of the required software.

Background and Objectives: The Rehabilitation Medicine Department provides psychiatric evaluation and treatment, physical therapy, occupational therapy, and speech therapy for NIH Clinical Center patients referred by Institute physicians. In addition, it develops various indices to evaluate these services. The department supports the efforts of and collaborates with Institute physicians engaged in research relevant to physical rehabilitation medicine. It also initiates both clinical and basic research independent of the Institutes in the rehabilitation of mentally and physically handicapped individuals.

In support of these goals, CSL is specifying a computer system for the Rehabilitation Medicine Department. Initially, the department will use the system for the following three projects:

1. The Physical Therapy Quality Assurance System--a data base system that will be used to: assess medical staff effectiveness in providing the types of patient care needed, determine staff workload and scheduling, and identify areas for clinical research for the Physical Therapy Service;

2. The Hand Dynamometer Instrument--a device that will be used to measure the magnitude and direction of the forces in the hand and to develop clinical tests to diagnose the mechanical and functional status of the hand, arm, and shoulder;

3. The Automated Biomechanics Laboratory--a system that will be used to automatically measure: the position of the limb segments in space, the forces in the lower limbs, and the electromyographic signals from the muscles in the limbs. The computer will perform measurement, analysis, display, and recordkeeping functions in these and future applications.

Significance to Biomedical Research: The computer system will be used with arthritic, orthopedic, and neurological patients, and with amputees in order to evaluate drug therapy, orthopedic and prosthetic devices, and medical interventions. It also will be used as a teaching tool to help these patients learn to function with their disability in an efficient manner. Many hospitals in the United States are presently establishing automated biomechanics and gait analysis laboratories. Therefore, any new developments made on this project will benefit users of these automated systems, as well as patient care

INFORMATIONAL INFORMATION (OPTIONAL) PROJECT NUMBER: 201 CT0082-01 CSL		TITLE OF PROJECT (100 characters or less) Image Processing of Electron Micrographs	
PERIOD COVERED October 1, 1980 to September 30, 1981			
NAME, LOCATION AND TELEPHONE NUMBERS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PERSONNEL ENGAGED IN THE PROJECT PI: B. L. Trus Research Chemist CSL, ORT OTHER: A. C. Steven Visiting Associate LRB, NIADOK A. A. Pier Chief LRB, NIDR			
COOPERATING UNIT (100 characters or less) LRB, NIADOK; LRB, NIDR			
LABORATORY Computer Systems Laboratory			
SECTION System Design Section			
PROJECT AND COOPERATING UNIT ORT, NIH, Bethesda, MD 20205			
TITLE ABSTRACT (100 characters or less) 0.6 0.6			
CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUE <input checked="" type="checkbox"/> (c) NUCLEAR			
SUMMARY (400 words or less - abstract required) This project, which was transferred from NIDR during this reporting period, is intended to design hardware and software mechanisms for the image processing and image reconstruction of electron micrographs. Computer software that has been developed to assist by a number of NIH research groups and programs have been exported to outside facilities. Under investigation at this time as part of this project are virus structures and collagen structures; other groups are looking at numerous other biological specimens such as keratin, membrane structure, immunoglobulin structure, and muscle structure.			

INFORMATIONAL INFORMATION (OPTIONAL) PROJECT NUMBER: 201 CT0083-01 CSL		TITLE OF PROJECT (100 characters or less) Positron Emission Tomography (PET) Scan Image Analysis in Aging Studies	
PERIOD COVERED October 1, 1980 to September 30, 1981			
NAME, LOCATION AND TELEPHONE NUMBERS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PERSONNEL ENGAGED IN THE PROJECT PI: James R. DeLo Computer Systems Analyst CSL, ORT Richard A. Margolin Senior Staff Fellow LN, NIA OTHER: Stanley J. Rapoport Chief LN, NIA			
COOPERATING UNIT (100 characters or less) Laboratory of Neurosciences (LN), NIA; Nuclear Medicine Department (NM), CC; Diagnostic Radiology (DR), CC			
LABORATORY Computer Systems Laboratory			
SECTION Systems Design Section			
PROJECT AND COOPERATING UNIT ORT, NIH, Bethesda, MD 20205			
TITLE ABSTRACT (100 characters or less) 0.2 0.2			
CHECK APPROPRIATE BOXES: <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUE <input type="checkbox"/> (c) NUCLEAR			
SUMMARY (400 words or less - abstract required) Exploration of the use of the combined power of Computer Assisted Tomography (CAT) scanning and Positron Emission Tomography (PET) scanning to study brain cell metabolism in diseases associated with aging is the purpose of this project. The initial goal is to provide a computerized image analysis procedure to delineate brain substructures represented in spatially sequenced CAT scan images and to determine metabolic activity in these substructures from corresponding sequenced PET scan images.			

and clinical research within the Rehabilitation Medicine Department at NIH.

Progress in FY81: CSL's collaboration with the Clinical Center's Rehabilitation Medicine Department began this year. Areas that could benefit from computer support were identified and specifications for the required computer hardware and software components were developed. CSL established the preliminary requirements for the department's computer system.

A large amount of specialized instrumentation is needed to perform the required automated measurements. The Biomedical Engineering and Instrumentation Branch of NIH's Division of Research Services built the hand dynamometer. CSL acquired information on commercially available force plates that are used to measure ground reaction forces and portable electromyogram telemetry units that transmit the muscle signals from the patient to the computer without any impeding cables. CSL also evaluated camera systems that can automatically measure body kinematics including the United Technologies Research Center infrared system, the Oxford Medical Systems strobe light system, and the Selcom Light Emitting Diode system.

Proposed Course: CSL will continue to offer advice regarding computer hardware and software, transducers, and instrumentation. Rehabilitation Medicine expects to purchase these components during the coming year.

Image Processing of Electron Micrographs

This project, which was transferred from NIDR during this reporting period, is intended to design hardware and software mechanisms for the image processing and image reconstruction of electron micrographs. Computer software that has been developed is used by a number of NIH research groups, and programs have been exported to outside facilities. Under investigation at this time as part of this project are virus structures and collagen structure; other groups are looking at numerous biological specimens such as keratin, membrane structure, immunoglobulin structure, and muscle structure.

Background and Objectives: The objective of this project is to develop a general-purpose software package for the analysis of electron micrographs. In addition, the computer analysis requires optimal utilization of the available hardware. These techniques and software have been used in independent applications by some researchers, and in collaborative projects by others.

Significance to Biomedical Research: Computer

analysis of electron micrographs is a relatively recent addition to the tools available for structural analysis. It is an extremely powerful technique when applied to two-dimensional crystalline structures, and can be used to correlate and align similar particles that are not crystalline. In addition, images can be corrected for a number of artifacts and experimental problems.

Progress in FY81: This project, which was begun in NIDR, has involved some growth in software and hardware methods, but primarily has grown in the utilization of programs and in the number of people who are using the software system PIC. In addition, use of Brookhaven STEM data is markedly increased. PIC has been expanded to interact with much of the general purpose image processing software in the image processing computer system.

Computer analysis of electron micrographs of beet necrotic yellow vein virus (BNYVV) has been completed. The structure is similar to that of tobacco mosaic virus (TMV), but important differences exist. The spatial arrangement of BNYVV RNA (49 residues per helical turn, pitch=2.6nm) is virtually identical to that of TMV (49 residues per turn, pitch=2.3nm). However, the helical packing of the protein coat is significantly different. The BNYVV protein has a helical packing of 49/4 subunits per turn and 4 bases per subunit while TMV has 49/3 subunits per turn and 3 boxes per subunit.

Proposed Course: This project will continue software development as needed, and will be converted to utilize the new image processing facility when it is available. In addition, because new biological structures are regularly available, these will be examined.

Publications:

Steven, A. C., Trus, B. L., Putz, C., and Wurtz, M.: The Molecular Organization of Beet Necrotic Yellow Vein Virus. *Virology* (in press).
Trus, B. L. and Steven, A. C.: Digital Image Processing of Electron Micrographs-The PIC System. *Ultramicroscopy* (in press).

Positron Emission Tomography (PET) Scan Images Analysis in Aging Studies

Exploration of the use of the combined power of Computer Assisted Tomography (CAT) scanning and Positron Emission Tomography (PET) scanning to study brain cell metabolism in disease associated with aging is the purpose of this project. The initial goal is to provide a computerized image analysis procedure to delineate brain substructures represented in spatially, sequenced CAT scan images and to determine metabolic activity in these substructures from corresponding sequenced PET scan images.

Background and Objectives: Positron Emission Tomography (PET) scanning performed in the Nuclear Medicine Department of the NIH Clinical Center provides a spatially sequenced series of images of regional cerebral glucose metabolism in man. The Laboratory of Neurosciences of the National Institute of Aging wishes to incorporate PET scanning technology in the study of disease associated with aging. The initial goal of this project is to delineate brain substructures represented in spatially sequenced Computer Assisted Tomography (CAT) scan images and to determine metabolic activity in these substructures from corresponding spatially sequenced PET scan images.

Methods Employed: Methods for establishing external coordinates to align corresponding PET and CAT scans are being investigated. Equations for converting radiation units to glucose utilization units are being finalized. Procedures for transporting PET scan and CAT scan images from the NIH Clinical Center to the DCRT Image Processing Facility have been established. Software is being written to determine statistical characteristics of PET scan regions of interest as delineated manually on corresponding CAT scan images.

Significance to Biomedical Research: It is anticipated that this work will provide a basis for evaluating the utility of PET scanning in studying diseases associated with aging. Successful implementation of an external coordinate system should provide for accurate anatomical region designation via higher resolution CAT scan images to measure physiological processes from corresponding lower resolution PET scan images.

Proposed Course: Upon implementation of an external coordinate device and finalization of radiation-to-glucose conversion equations, analysis will commence.

MEDICINE (GENERAL INFORMATION) (ADDRESS) PROJECT NUMBER (DO NOT USE THIS ADDRESS)		HEALTH, EDUCATION, AND WELFARE DEPARTMENT OF PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00084-01 CSL	
PERIOD COVERED October 1, 1980 to September 30, 1981					
TITLE OF PROJECT (DO NOT USE THIS ADDRESS)					
Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies					
NAME, LASTNAME, AND INITIALS OF PRINCIPAL INVESTIGATOR AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI: James M. DeLeo		Computer Systems Analyst		CSL, DCRT	
OTHER: Brad Thompson		Research Associate		LB, C	
COOPERATING UNITS (IF ANY)					
Laboratory of Biology (LB), C					
LABORATORY					
Computer Systems Laboratory					
SECTION					
Systems Design Laboratory					
INSTITUTION AND LOCATION					
DCRT, NIH, Bethesda, MD 20205					
TOTAL WATERMARK: 0.5		PROFESSIONAL: 0.5		OTHER:	
OTHER APPROPRIATE (CHECK)					
<input checked="" type="checkbox"/> (a) HUMAN TISSUES <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) OTHER					
<input type="checkbox"/> (d) MIND <input type="checkbox"/> (e) INTERVIEW					
SUMMARY OF WORK (DO NOT USE THIS ADDRESS)					
A computerized methodology for analyzing autoradiographic spot images associated with recombinant DNA bacterial colonies has been developed in collaboration with scientists at NCI. This system represents a unique refinement in a method to directly identify cloned sequences complementary to messenger RNA that are developmentally or hormonally induced. Spot density measurements are computed from digitized images produced via microdensitometry. These measurements are corrected for variability in exposure and local background, calibrated to hybridization standards, and normalized for comparison purposes. The system provides a variety of graphical and tabulation output that effectively summarizes experimental results and identifies significant induced hybridization events.					

ML-100-1
(Rev. 10-79)

MEDICINE (GENERAL INFORMATION) (ADDRESS) PROJECT NUMBER (DO NOT USE THIS ADDRESS)		HEALTH, EDUCATION, AND WELFARE DEPARTMENT OF PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00085-01 CSL	
PERIOD COVERED October 1, 1980 to September 30, 1981					
TITLE OF PROJECT (DO NOT USE THIS ADDRESS)					
Cataract Grading via Computerized Slit-lamp Image Analysis					
NAME, LASTNAME, AND INITIALS OF PRINCIPAL INVESTIGATOR AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI: James M. DeLeo		Computer Systems Analyst		CSL, DCRT	
OTHER: Robert D. Sperduto Leo T. Chylack, Jr.		M.D., Chief, Division of Ophthalmology Harvard Medical School		BE, NEI	
COOPERATING UNITS (IF ANY)					
Office of Biometry & Epidemiology (BE), NEI Division of Ophthalmology, Harvard Medical School					
LABORATORY					
Computer Systems Laboratory					
SECTION					
Systems Design Section					
INSTITUTION AND LOCATION					
DCRT, NIH, Bethesda, MD 20205					
TOTAL WATERMARK: 0.2		PROFESSIONAL: 0.2		OTHER:	
OTHER APPROPRIATE (CHECK)					
<input checked="" type="checkbox"/> (a) HUMAN TISSUES <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) OTHER					
<input type="checkbox"/> (d) MIND <input type="checkbox"/> (e) INTERVIEW					
SUMMARY OF WORK (DO NOT USE THIS ADDRESS)					
The aim of this project is to develop an objective cataract grading scheme, a goal having high priority among cataract researchers. Slit-lamp camera images of the human eye lens are entered into the DCRT Image Processing system via microdensitometry methods. A method for quantitating opacity along the visual axis for purposes of comparing similar images of a given lens has been developed. Early results demonstrate the need for improved quality control in image preparation to assure the success of the methodology. Experiments are being conducted to further determine the accuracy limitations of this approach.					

ML-100-1
(Rev. 10-79)

Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies

A computerized methodology for analyzing autoradiographic spot images associated with recombinant DNA bacterial colonies has been developed in collaboration with scientists in NCI. This system represents a unique refinement in a method to directly identify cloned sequences complementary to messenger RNA that are developmentally or hormonally induced.

Spot density measurements are computed from digitized images produced via microdensitometry. These measurements are corrected for variability in exposure and local background, calibrated to hybridization standards, and normalized for comparison purposes. The system provides a variety of graphical and tabulation output that effectively summarizes experimental results and identifies significant induced hybridization events.

Background and Objectives: NCI scientists have been refining techniques to directly identify cloned sequences complementary to messenger RNA that are developmentally or hormonally regulated. This refinement has led to a methodology which produces autoradiographic spot images representative of cell colony hybridization. The objective of this project is to provide an automated procedure for a quantitative analysis of understanding of these images.

Methods Employed: Radioactively-induced cell colonies are placed into microtiter wells, grown on agar, transferred to filter paper, and hybridized to end-labeled mRNA or cDNA probes. Autoradiographs of the filters are digitized and the density of each spot relative to background is established by means of CSL-developed image processing software operational on the DCRT Evans and Sutherland PDP-11/70 computer system. Compensation for variations in background, film exposure conditions, and hybridization are included in the methodology. A variety of graphical output including scatter diagrams, histograms, and listings is provided.

Significance to Biomedical Research: Classical solution hybridization techniques are too cumbersome to be performed en masse. The methodology developed allows quantitative hybridization studies on a large number of sequences. Earlier qualitative assessment of autoradiographic spot images is now superseded with automated procedures yielding more accurate, more reproducible data. Computer graphic presentation of results greatly facilitates identification of significant experimental events.

Proposed Course: Production image analysis has started and will continue. Further software refinements, to include more complete automated analysis and new graphics software, are planned.

Cataract Grading via Computerized Slit-lamp Image Analysis

The aim of this project is to develop an objective cataract grading scheme--a goal having high priority among cataract researchers. Slit-lamp camera images of the human eye lens are entered into the DCRT Image Processing System via microdensitometry methods. A method for quantitating opacity along the visual axis for purposes of comparing similar images of a given lens has been developed. Early results demonstrate the need for improved quality control in image preparation to assure the success of the methodology. Experiments are being conducted to further determine the accuracy limitations of this approach.

Background and Objectives: A major problem for cataract researchers has been the lack of an objective, reproducible in vivo cataract classification scheme. Subjective classification methods are currently depended upon. With the tremendous variability in the morphology of cataracts, it is difficult to rely on such methodology either in survey work or in longitudinal studies. Development of an objective cataract grading scheme is seen as a high priority item among cataract researchers.

Methods Employed: Images of the human eye lens obtained from Topcon and Zeiss slit-lamp cameras are digitized via microdensitometry and the resultant qualified image representations are entered into the DCRT Image Processing System for analysis. Analysis consists of computing a histogram of the density(opacity) values within a narrow band centered about the visual axis. The resultant histogram is partitioned into five equal bands and a corresponding color isodensitometric image is displayed. A quantitative distribution of percent involvement for each of the five bands is also provided. Time-spaced images of the same eye lens may be compared with these results to track disease progression or regression.

Major Findings: The interactive computer system developed for quantitating visual axis opacity is operational and easy to use. Analysis of initial prototype images suggests the need for improved quality control in all aspects of image preparation.

Significance to Biomedical Research: Development of an objective cataract grading scheme is seen as a high priority item among cataract researchers.

Proposed Course: Studies on a larger population of images are planned. These studies should result in procedures to facilitate image comparison. The studies should also provide accuracy measurements for variables introduced by factors such as camera type, photographic procedures, microdensitometry procedures, and computer analysis.

NIH INTRACENT CLINICAL RESEARCH PROGRAM
 PROJECT NUMBER (SEE NIH FORM 100-100) 201 CT00076-02 CSL
 TITLE OF PROJECT (30 characters or less)
 TITLE OF PROJECT (30 characters or less)

PERIOD COVERED: October 1, 1980 to September 30, 1981

Image Analysis in Computerized Tomography (CT) Contrast Material Evaluation

PI: James M. Dileo Computer Systems Analyst CSL, DCRT
 Michael Verness Radiologist DR, CC

NAME, ADDRESS AND PHONE NUMBER, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONNEL PERSONNEL INVOLVED IN THE PROJECT

CREATING UNIT (14 x 7)

Diagnostic Radiology (DR), CC

Computer Systems Laboratory

Systems Design Section

INSTITUTION AND LOCATION

DCRT, NIH, Bethesda, Maryland 20205

TOTAL BUDGET

0.1

NON-FEDERAL

0.1

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Image Analysis in Computerized Tomography (CT) Contrast Material Evaluation

The intent of this project is to provide a tool for the quantitative analysis of liver and spleen section of computerized tomograms (CT) to demonstrate efficacy of a new experimental contrast material that was developed at the NIH Clinical Center as an aid in the demonstration of early metastatic disease of the liver. Software for performing this analysis is fully operational on the Image Processing System. Measurements have been made on pre- and post-injection tomograms. Several classical image texture measurements are being tried as discriminating features in the demonstration of contrast material effectiveness.

Background and Objectives: The objective of this project is to provide a procedure for performing statistical analysis of attenuation values lying within any specified closed amorphous contour of computerized tomogram (CT) images. This procedure is to be used for quantitative analysis of liver and spleen sections of CT images in order to demonstrate the efficacy of a new experimental contrast material that was developed at the NIH Clinical Center to aid the demonstration of early metastatic disease of the liver.

Methods Employed: CT images are transported by means of magnetic tape from the Diagnostic Radiology Department (DR) of the Clinical Center to the Image Processing Facility in DCRT. Interactive software has been written and implemented to read the CT images from magnetic tape, draw selected contours to indicate areas of interest, and perform statistical analysis on the attenuation values within the chosen areas. Liver and spleen sections of pre- and post-injection images are processed and compared.

Significance to Biomedical Research: Most current CT computer systems provide limited statistical analysis within small fixed-shape contours (circles or squares). The approach presented here offers unlimited analysis within any shape contour. The software may be easily extended to measure other features based on groupings of attenuation values; such features could be useful in further differentiating image elements and diseased areas. The software has obvious extension to the analysis of other types of biomedical images.

Proposed Course: Analysis of liver and spleen sections on pre- and post-injection tomograms are continually being performed as images are made available. It is intended to explore the usefulness of several classical image texture measurements in the demonstration of contrast material effectiveness.

PERIOD COVERED: October 1, 1980 to September 30, 1981
 TITLE OF PROJECT (in characters of text):
 Image Analysis in Automated Radiotherapy Treatment Planning

PI: James M. Deleo Computer Systems Analyst CSL, DCRT
 Eli Glatstein Chief RD, NCI

COOPERATING UNIT (s):

Radiation Oncology Branch (RD), NCI

Computer Systems Laboratory

Systems Design Section

INSTITUTION AND LOCATION

NCI, NIH, Bethesda, Maryland 20205

TOTAL PERSONNEL:

0.0

CHECK APPROPRIATE BOXES:

(X) (a) MANUSCRIPT (b) INTERVIEW

(c) OTHER

(d) OTHER

(e) OTHER

(f) OTHER

(g) OTHER

(h) OTHER

(i) OTHER

(j) OTHER

(k) OTHER

(l) OTHER

(m) OTHER

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Image Analysis in Automated Radiotherapy Treatment Planning

This project is directed towards finding improved methods of analyzing computerized tomography (CT) images in order to provide optimal methods of automated radio therapy treatment planning. Various algorithms for contrast enhancement, contour detection, extraction, following, coordinate data compression, and three-dimensional representation have been implemented and tested. The project has been inactive during the past year.

Background and Objectives: The objective of this project is to find improved computerized methods for isolating specific organs and diseased areas in computerized tomography (CT) images for the purpose of improving upon computer-assisted methods of radiotherapy treatment planning.

Methods Employed: CT scans are transported by magnetic tape to the Evans and Sutherland System in DCRT, where they are entered and analyzed. Analysis consists of applying a variety of classical and experimental algorithms for contrast enhancement, density slicing, texture analysis, contour detection, contour extraction, contour following, contour coordinate data compression, and three-dimensional reconstruction.

Significance to Biomedical Research: Improvements in computer-assisted radiotherapy treatment planning should result in improved patient care.

Proposed Course: Plans for future work have not been specified at the time of this writing.

Automated Pulmonary Physiology Testing

Procedures such as exercise testing, pulmonary compliance, and work of breathing have been found successful for evaluating pulmonary function. By exercising a patient on a treadmill and gradually increasing the workload (i.e., speed and incline), the physician can better assess cardio-pulmonary disease, which in its early stages generally does not manifest itself except under physical exertion. In order to help the physician perform these procedures more effectively, a microcomputer system has been developed to enable automated realtime collection, analysis, and display of pulmonary compliance data. Work is in progress to complete an automated exercise procedure as well. Data is stored in a local disk data base for future reference.

Background and Objectives: Physicians monitor pulmonary parameters during exercise to better assess pulmonary function and to diagnose pulmonary dysfunction that only manifests itself

under physical exertion. Procedures such as pulmonary compliance and inspiratory muscle strength also give insight into respiratory function.

Until recently, pulmonary treadmill exercise testing was performed manually at NIH. Data were written down and later entered into a programmable calculator for determination of results. Additional summary statistics and a final report were prepared by hand. Work of breathing and pulmonary compliance measurements, done in the same lab, were likewise performed manually.

In order to speed both exam and data analysis time, and to improve accuracy, these procedures are being automated with a microcomputer system.

Methods Employed: The microcomputer system is a DEC MINC-11/03 (Modular Instrument Computer) containing an LSI-11 microprocessor, 32K words of memory, auxiliary disk storage, and analog-to-digital and digital-to-analog conversion capability. There is also a video graphics display, a keyboard console, a hard copy unit for printing the video display, and a line printer.

In determining pulmonary compliance, transpulmonary pressure (the difference between alveolar pressure, i.e., mouth pressure with mouth shutter closed, and esophageal pressure, as measured by a balloon transducer swallowed by the patient) and lung volume (measured with a wedge spirometer) are determined by the computer as the physician repeatedly closes a mouth shutter throughout a patient's inhalation or exhalation. A graphical plot of the data is then produced to aid in evaluating the 'stretchability' of the patient's lungs.

In a similar manner, a patient's relative inspiratory muscle strength is determined by measuring the most negative pressure developed when inspiring against a closed mouth shutter.

During the treadmill exercise procedure, the computer monitors expired volume and flow via a Tissot spirometer and pneumotach, respectively. Inspired and expired oxygen, carbon dioxide, and nitrogen concentrations are monitored via a Perkin Elmer mass spectrometer gas analyzer. Acid/base and gas concentrations are determined offline from a sample of the patient's arterial blood, and entered at the keyboard. Pulmonary volumes, flows, and oxygen consumption--a measure of how hard the patient actually works to perform a given level of exercise--are then calculated.

Progress in FY81: The MINC-11 microcomputer and related peripherals were installed and functioning by November 1980. The manual data

entry exercise analysis package developed earlier on the CSL LSI-11/03 development system was directly transferred to the MINC, immediately enabling the automatic processing of exercise data. Due to a change in clinical priorities, it was decided to first automate the compliance and inspiratory muscle strength tests, and then proceed further with the exercise protocol.

Utilizing the MINC's realtime data acquisition and graphics capabilities, subsequently, software was developed to enable a full automation of the compliance and inspiratory muscle strength procedures. Only minimal modifications to the existing pulmonary hardware were required. In addition to the capabilities for data acquisition, analysis, and display, a scheme for storing data locally on disk allowing subsequent retrieval was developed. Later on, the stored data will be incorporated with the central pulmonary data base being developed by DMB.

Proposed Course: First, the existing exercise protocol will be completed. Then, having automated all existing pulmonary lab procedures, we will use the computer for work that could not be done by manual methods. For example, we plan to include closed loop computer control of treadmill speed. By monitoring heart rate and dynamically varying the treadmill speed, it should be possible to apply a more constant workload to the patient, thus leading to more stable results. In addition to performing more complicated laboratory procedures, additional forms of mathematical analysis will be applied to the data in order to gain further insight into the patient's pulmonary function. Having developed a general-purpose tool for pulmonary data collection, it will be this latter portion of the project that has the potential for advancing the state-of-the-art in pulmonary medicine.

Publications:

Nadel, L. D.: Automated Pulmonary Analysis by an On-line Microcomputer.
In Nair, S. (Ed.): *Proceedings of the Conference on Computers in Critical Care and Pulmonary Medicine*. New York, Plenum Press (in press).

MULTIDISCIPLINARY SCIENCE INSTRUMENTATION (MDSI) PROJECT NUMBER (SEE MDSI FOR THIS FORM)		NIAH DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE OFFICE OF INTRAMURAL RESEARCH PROJECTS		PROJECT NUMBER Z01 CT 00060-02 CSL
PERIOD COVERED October 1, 1980 to September 30, 1981				
TITLE OF PROJECT (NO CHARACTER LIMITS) Measurement of Transepithelial Resistance of Kidney Tubule				
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT				
PI:	Susan Hauser	Electronics Engineer	CSL, DCR7	
OTHER:	Antonio Almeida	Visiting Fellow	LRHM, NHLBI	
COOPERATING UNITS (IF ANY)				
Laboratory of Kidney and Electrolyte Metabolism, NHLBI				
Computer Systems Laboratory				
Project Development Section				
INSTITUTION AND LOCATION DCR7, Bldg. Bethesda, Maryland 20205				
TOTAL BUDGET 0.3		PROFESSIONAL 0.3		
OTHER APPROPRIATE BUDGETS 0.3		OTHER 0.3		
(a) FUNDING AGENCIES (b) FUNDING TITLES (c) FUNDING NUMBERS		(d) FUNDING NUMBERS		
A microcomputer-based instrument was developed in FY80 to facilitate determination of the transepithelial resistance of an in vitro preparation of a kidney tubule. The instrument controls the onset, intensity, and duration of a series of electric current pulses through the preparation, measures the induced voltage changes, and prints those values. The instrument was upgraded in FY81 to include online calculation of the transepithelial resistance and other parameters of interest.				
PREPARED BY (NAME AND TITLE)				

Measurement of Transepithelial Resistance of Kidney Tubule

A microcomputer-based instrument was developed in FY80 to facilitate determination of transepithelial resistance of an in vitro preparation of kidney tubule. The instrument controls the onset, intensity, and duration of a series of electric current pulses through the preparation; measures the induced voltage changes; and prints those values. The instrument was upgraded in FY81 to include online calculation of the transepithelial resistance and other parameters of interest.

Background and Objectives: The objective is to automatically measure the transepithelial resistance of in vitro preparations of kidney tubule. A microprocessor-based instrument was developed to facilitate these measurements. Based on operational directives entered by the user, the instrument controls the polarity, duration, and intensity of each of a series of current pulses through the tubule preparation, and determines and records the steady state voltages induced at either end of the preparation. Transepithelial resistance and other parameters are calculated from these values.

Significance to Biomedical Research: Previous manual methods for obtaining these measurements were time-consuming and prone to error. With the control instrument, a complete set of measurements can be made in a few moments. The experiment can easily be rerun under the same or a different set of conditions to test repeatability and consistency.

Progress in FY81: The capability to calculate the resistances and other parameters using a complex set of equations derived from a transmission line model was added to the instrument. This was accomplished by adding floating point math hardware and software to utilize it. The calculated values for every current pulse are now available to the investigator immediately following execution of the pulse sequence. Of particular interest is the immediate display of the tubule diameter. A close correspondence of the calculated diameter with the actual diameter indicates that the preparation is intact and that other calculations are valid.

Proposed Course: We may make a few minor software changes to tailor the instrument's user-interaction features to this experiment. No major effort is anticipated for the future.

Publications:

Hauser, S. E. and Almeida, A.: A Control and Data Processing Instrument for Kidney Tubule Research. *Biomedical Sciences Instrumentation* 17: 13-19, 1981.

Electron Microanalysis Facility

CSL in collaboration with BEIB is developing an automated electron microanalysis facility consisting of two electron microscopes interfaced to a computer system. The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL is designing and implementing the computer system, which will acquire and display the spectra and images produced by Electron Energy Loss Spectrometry, Energy-Dispersive X-ray Spectrometry, and Wavelength-Dispersive X-ray Spectrometry.

See also:

Z01 RS 10058-03

Z01 RS 10059-03

Z01 CT 00042-03

Background and Objectives: The Computer Systems Laboratory is designing and implementing a computer system as part of the BEIB Microanalysis Facility. The facility consists of two electron microscopes, and will be used for research into the elemental composition of biological specimens and for developing new techniques in electron microscopy. Work on this project is now in its third year.

One of the electron microscopes is an Hitachi H-700H 200 keV Scanning Transmission Electron Microscope (STEM) equipped with:

- a lithium-drafted silicon [Si(Li)] detector connected to a Kevex 7000 Analytical Spectrometer for performing Energy-Dispersive X-ray Spectrometry (EDS);
- an electron spectrometer for performing Electron Energy Loss Spectrometry (EELS); and
- detectors for forward-scattered, back-scattered, secondary, and sample electron current signals.

The other electron microscope is a Cameca 50 keV Electron Microprobe equipped with:

- an Si(Li) detector for performing EDS;
- three Wavelength Dispersive X-ray (WDS) spectrometers; and,
- detectors for forward-scattered, back-scattered, secondary, and sample electron current signals.

A PDP-11/60 computer system ultimately will be interfaced to both microscopes to perform the following functions:

- control electron beam position, stage position, and the various detectors;
- acquire spectra and image data from all detectors;

PROJECT INFORMATION SHEET
PROJECT NAME: ELECTRON MICROANALYSIS FACILITY
PROJECT NUMBER: Z01 CT 00061-02 CSL
PROJECT STATUS: IN PROGRESS
PROJECT START DATE: October 1, 1980 to September 30, 1981
PROJECT END DATE: September 30, 1981

PROJECT DESCRIPTION: Electron Microanalysis Facility
The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL is designing and implementing the computer system, which will acquire and display the spectra and images produced by Electron Energy Loss Spectrometry, Energy-Dispersive X-ray Spectrometry, and Wavelength-Dispersive X-ray Spectrometry.

PERSONNEL:

NAME	POSITION	DEPARTMENT
C. E. Fiori	Physical Scientist	BEIB, ORS
A. E. Gorlen	Electronics Engineer	CSL, DCR
L. A. Barden		CSL, DCR
J. S. del Priore		CSL, DCR
P. S. Plexico		CSL, DCR
M. A. Douglas		LAS, DCR
E. W. Pittala		LAS, DCR
C. G. Gibson		BEIB, ORS
R. D. Lohman		BEIB, ORS
A. F. Leroy		BEIB, ORS
C. R. Jeyl		BEIB, ORS

PROJECT LOCATION: NUBI, NADON, NIMH, NINCOS
Computer Systems Laboratory
Project Development Section
PDP-11, Bethesda, MD, 20805

PROJECT BUDGET: \$2
PROJECT FUNDING: \$2

PROJECT STATUS: IN PROGRESS

PROJECT DESCRIPTION: CSL in collaboration with BEIB is developing an automated electron microanalysis facility consisting of two electron microscopes interfaced to a computer system. The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL is designing and implementing the computer system, which will acquire and display the spectra and images produced by Electron Energy Loss Spectrometry, Energy-Dispersive X-ray Spectrometry, and Wavelength-Dispersive X-ray Spectrometry.

See also: Z01 RS 10058-03
Z01 RS 10059-03
Z01 CT 00042-03

PROJECT INFORMATION SHEET
PROJECT NAME: COMPUTER ASSISTANCE FOR BLIND COMPUTER USERS
PROJECT NUMBER: Z01 CT00063-02 CSL
PROJECT STATUS: IN PROGRESS
PROJECT START DATE: October 1, 1980 to September 30, 1981
PROJECT END DATE: September 30, 1981

PROJECT DESCRIPTION: Computer Assistance for Blind Computer Users
We have developed a voice output terminal for use by blind computer professionals. Full word unlimited vocabulary speech output is made possible by combining a voice synthesizer with a text-to-speech program running in a micro-computer. We are working with our blind users to develop additional techniques for presenting visual data in audible form.

PERSONNEL:

NAME	POSITION	DEPARTMENT
Scott J. Allen	Medical Research Analyst	CSL, DCR
David C. Sompco	Electronics Engineer	CSL, DCR
Perry S. Plexico	Chief, Project Development Section	CSL, DCR
David M. Staffel	Computer Programmer	CSL, DCR

PROJECT LOCATION: NUBI, NADON, NIMH, NINCOS
Computer Systems Laboratory
Project Development Section
PDP-11, Bethesda, MD, 20805

PROJECT BUDGET: \$2
PROJECT FUNDING: \$2

PROJECT STATUS: IN PROGRESS

PROJECT DESCRIPTION: We have developed a voice output terminal for use by blind computer professionals. Full word unlimited vocabulary speech output is made possible by combining a voice synthesizer with a text-to-speech program running in a micro-computer. We are working with our blind users to develop additional techniques for presenting visual data in audible form.

- process and display the spectra and image data;
- monitor and display a wide variety of 'housekeeping' parameters, including: lens currents, lens temperatures, beam current, beam energy, pump temperatures, coolant flow rates, vacuum pressures, water leak detectors, floor vibrations, ambient AC fields, power supply voltages, room temperature, and room humidity.

Progress in FY81: CSL's software efforts this year have been concentrated on four aspects of data acquisition from the STEM:

1. acquisition of EELS spectral data and control of STEM beam position,
2. acquisition, calibration, monitoring, and display of housekeeping parameters,
3. retrieval of empirical X-ray information, and
4. installation and programming of the color display systems.

EELS data acquisition and control of the STEM beam position is done by a satellite processor connected to the PDP-11/60 by a high-speed link. Software has been written that allows the STEM operator to define areas of a specimen as targets for data acquisition and to collect EDS, EELS, and electron current signal data from the target areas. The data is acquired in SPECTRUM mode, which produces a single X-ray and/or EEL spectrum from the target area along with as many as four electron current signal images.

EDS data acquisition is done by the KeveX 7000, which is connected directly to the computer. Software has been developed to: allow programs on the 11/60 to directly communicate with and control the KeveX 7000; save or restore spectra and associated information to or from user library files; allow programs on the 11/60 to access, insert, or delete spectra contained in user library files. This software is currently being used by BEIB scientists for research into methods of processing EDS and EELS spectra to remove background and resolve overlapping peaks/edges.

Housekeeping parameters are acquired by the computer by means of an Analogics AN5400 data acquisition subsystem. Software has been developed to acquire, monitor, and display these parameters.

Calibration parameters for housekeeping and other signals are managed by a Calibration Utility that was developed this year. This utility maintains calibration information on a disk file and allows it to be listed, updated, and restored to memory-resident tables at system boot.

To simplify the operation of the data acquisition and

display software that is being developed, a menu selection scheme is used. The menu selection software is completely table-driven so that it is easy to add new functions as they become available. Currently, the housekeeping parameter display and specimen target definition functions can be activated through menu selection.

Work has begun on software to retrieve information associated with X-ray emitting electron energy transitions within atoms. This software will allow an operator or another program to specify an element and the transition(s) of interest using a convenient notation. It will then look up the associated transition energies and relative peak amplitudes. Conversely, an energy range may be specified, in which case a list of the transitions within that range will be retrieved. This work is being done under contract by Systex, Inc.

A DeAnza ID5400 color display system was delivered in October 1980 and was successfully interfaced to the PDP-11/60. Work has begun on software to support image display and processing.

A second satellite processor for interfacing the microprobe to the computer was delivered in FY81 and is currently connected to CSL's PDP-11/70 system where it is used for development of software for the STEM satellite.

Proposed Course: Next year, we expect to:

- implement additional modes of acquisition for EELS and EDS spectra and images and the four electron current signals from the STEM;
- have a package to facilitate the display and processing of EDS, EEL, and electron current signal images on the DeAnza display system;
- begin work on the Cameca microprobe interface.

Computer Assistance for Blind Computer Users

We have developed a voice output terminal for use by blind computer professionals. Full word unlimited vocabulary speech output is made possible by combining a voice synthesizer with a text-to-speech program running in a microcomputer. We are working with our blind users to develop additional techniques for presenting visual data in audible form.

Background and Objectives: In previous years we have developed a voice output terminal that combines unlimited vocabulary with extensive text review capabilities. Three terminals were provided to different Government agencies and proved to be a valuable asset to the visually impaired computer professionals who used them. Similar voice output terminals are now marketed by the private sector. At least two of these are based on CSL work.

REPORT NUMBER: 201 CT00062-02 CSL
 TITLE: METABOLIC ENERGY MEASUREMENTS
 PROJECT NUMBER: 201 CT00062-02 CSL

PERIOD COVERED: October 1, 1980 to September 30, 1981
 TITLE OF PROJECT (NO characters or less)

Metabolic Energy Measurements

NAME, ADDRESS AND INSTITUTION, AFFILIATIONS, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONS WHOSE NAMES ARE LISTED ON THE PROJECT

PI: D. C. Sengco Electronics Engineer CSL, DCRB
 OTHER: R. W. Hendler Chief, MES LC, IR, NHLBI

NAME OF THE INSTITUTION
 Name

Computer Systems Laboratory

Project Development Section

DCRB, NIH, Bethesda, MD 20205

INVESTIGATOR'S ADDRESS: 0.5 (NAME) (TITLE)

PROJECT NUMBER: 201 CT00062-02 CSL

A microcomputer-based instrument was developed to study energy transduction phenomena of respiring membranes. Electrodes are interfaced to the microcomputer to measure concentrations of specific ions, of protons, and of oxygen. Programs are being developed to assay the change in pH across the membrane and the ratios of ion movements to oxygen uptake.

REPORT NUMBER: 201 CT00065-02 CSL
 TITLE: MEDICAL INFORMATION TECHNOLOGY PROJECT
 PROJECT NUMBER: 201 CT00065-02 CSL

PERIOD COVERED: October 1, 1980 to September 30, 1981
 TITLE OF PROJECT (NO characters or less)

Medical Information Technology Project

NAME, ADDRESS AND INSTITUTION, AFFILIATIONS, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONS WHOSE NAMES ARE LISTED ON THE PROJECT

PI: David C. Sengco Electronics Engineer CSL, DCRB
 Scott I. Allen, M.D. Medical Research Analyst CSL, DCRB

OTHER: Crawford S. Brown, M.D. Consulting Dermatologist CSL, DCRB
 David M. Stoffel Computer Programmer CSL, DCRB
 Perry S. Flexico Chief, Project Development CSL, DCRB
 A. W. Pratt, M.D. Director, DCRB

NAME OF THE INSTITUTION
 Computer Systems Laboratory

Project Development Section

DCRB, NIH, Bethesda, MD 20205

INVESTIGATOR'S ADDRESS: 2.0 (NAME) (TITLE)

PROJECT NUMBER: 201 CT00065-02 CSL

This project involves the application of microprocessor technology and improved man-machine interface methods to permit physicians and their associates to more directly communicate with computer record systems. This year we have begun implementation of concepts developed in previous years. A pilot study involving medical record keeping by direct input of examining physicians and staff is underway.

Progress in FY81: This year saw rapid developments of voice synthesis technology which resulted in the availability of integrated circuits, costing less than one hundred dollars, for the synthetic generation of English phonemes. We have incorporated these devices into our voice output terminal. This has resulted in not only reduced size and cost of the units but in enhanced capabilities in terms of rate of speech and intelligibility.

Proposed Course: Prior work, both by CSL and the private sector, has concentrated on the presentation of sequential, linear text in audible form. We plan additional studies in cooperation with our blind user-colleagues aimed at presenting text in other formats commonly employed on computers. Examples include tables, forms, and lists.

Metabolic Energy Measurements

A microcomputer-based instrument was developed to study energy transduction phenomena of respiring membranes. Electrodes are interfaced to the microcomputer to measure concentrations of specific ions, of protons, and of oxygen. Programs are being developed to assay the change in pH across the membrane and the ratios of ion movements to oxygen uptake.

Background and Objectives: CSL has collaborated with the LC, IR, NHLBI for a number of years in the development of new techniques for the study of bioenergetics. This effort began with the development of the Potentiometric Titration Controller, which continues to be used in the investigation of energy transfer phenomena at the energy parameters of respiring membranes. To be included are determinations of membrane potential and the concentrations gradient for protons across the membrane. New methods are also being developed to measure the rate of oxygen uptake and the ratio of protons and other ion movements to the atoms of oxygen consumed.

Progress in FY81: The microcomputer system designed in FY80 has been installed. A single board microcomputer was used in conjunction with a 6-channel D/A converter and a 16-channel A/D converter with programmable gain. A high speed mathematics module was interfaced to the system to enhance realtime calculations. As proposed last year, the data acquisition and control software were developed on the disk-based Potentiometric Titration Controller system and down-loaded to the target system. By utilizing the existing development facilities, only the hardware specific to the new experiments needed to be purchased.

An electrode was constructed specifically for the membrane-soluble probe, tetraphenylphosphonium (TPP), and this electrode has been shown to exhibit Nernstian behavior in the measurement of low concentrations of TPP in solution. A program has been developed which calculates in realtime the electric potential across a respiring membrane based on the internal volume of membrane vesicles in the suspension being analyzed, the external volume of the solution, and the voltage sensed by the TPP specific electrode. The membrane potential measured by this procedure has been found to agree with that determined by the traditional technique of flow dialysis, which is much more cumbersome and time-consuming.

Proposed Course: Development of the system to determine energy parameters of respiring membranes by use of electrodes will continue. Emphasis will be placed on using the pH and oxygen electrodes to assay the change in pH across the membrane and the ratios of ion movements to oxygen uptake.

Medical Information Technology Project

This project involves the application of microprocessor technology and improved man-machine interface methods to permit physicians and their associates to more directly communicate with computer record systems. This year we have begun implementation of concepts developed in previous years. A pilot study involving medical recordkeeping by direct input of examining physicians and staff is underway.

Background and Objectives: The use of computers within the biomedical community is increasing as the cost of systems is decreasing due to technological innovation. Enhancements in the area of man-machine interfaces must keep pace with the rapid advance of computer hardware and software technology. With this in mind, we have investigated devices, methods, and structures that could provide a more human-oriented interface while maintaining an acceptable level of flexibility and efficiency.

Progress in FY81: This year we have identified an area in which we can apply concepts developed in previous years. In collaboration with a practicing dermatologist, we have begun the development of a clinical care system which will allow the physician to store and retrieve the data contained in a medical record. This data includes histories, physical examinations, progress notes, treatments, and procedures.

The immediate objective of the pilot study underway

is to provide the physician with rapid and simple access to a dedicated microcomputer system. Disease-specific and problem-specific forms and protocols are used to prompt the user through the hierarchy of programs available. Much of the software is table-driven to allow the physician to add and modify not only the data base but the logic of the presentation. This approach also provides a convenient means of adapting the programs to other clinical care and research protocols. To support this effort, we are working in two main areas. The clinicians are designing the disease-specific protocols and formats as well as a general workup logic. The computer programmers are developing a generalized software system to provide a convenient, assistive interface for physicians to use. This software will aid the physician in accessing and selecting data from complex tree-structured files, and in entering data via a CRT terminal by simple menu selection for form fill-out methods.

Proposed Course: Both the clinical forms and clinical data access software are being developed on the CSL time-shared computer system. Online program trials from the dermatologist's office are in progress. We expect to be able to transfer operations of the software to a dedicated microcomputer system situated in the physician's office by the first quarter of FY82. At a later time, we plan to perform experiments using a touch screen, bar codes, and special cursor controls for data selection and entry.

Laboratory of Applied Studies

Eugene K. Harris, Chief

Summary of Activities

Computer-aided analysis of electrocardiograms. J. Bailey, M. Horton (LAS); cardiologists and biomedical engineers in the U.S.A., and abroad. To evaluate the utility of leading computer programs for ECG interpretation, and to search for optimal computer-based methods of extracting medically significant ECG patterns. A Comparison of IBM and GRI (Glasgow Royal Infirmary) ECG programs, including clinical documentation and semantic equivalences of output statements, has been published. A study of serial ECG's has begun jointly with staff of the Framingham Heart Study, NHLBI.

Computer systems for nuclear medicine. J. Bailey, M. Douglas, and others (LAS); H. Ostrow (CSL); M. Green, et al. (CC, Nuclear Medicine). Development and application of computer systems to such diagnostic imaging activities as ECG-gated radionuclide angiocardiology, functional mapping, and other scintigraphic studies of the kidney, brain, heart, and lung. In collaboration with Nuclear Medicine (CC) and the Cardiology Branch (NHLBI), various parameters measuring regional heart wall mobility are being studied for their discriminating ability in normal volunteers and heart patients. Data collection in the renal scintigraphy study to detect arterial stenosis in dogs has been completed. Results are now being analyzed and written for publication.

Computer-based studies of pulmonary pathophysiology and respiratory disease. J. Bailey, R. Burgess, and others (LAS); R. Crystal, A. Nienhuis (NHLBI); A. Jones (CC, Nuclear Medicine). To achieve better understanding of pulmonary pathophysiology through use of computer-based models of pulmonary gas exchange and respiratory mechanics, comparing predicted values with real patient data. A joint study of gas exchange in normal volunteers and patients at rest or exercising has advanced with development of a reliable gas analysis system and receipt of computer-controlled exercise test equipment.

Statistical research in clinical pathology. E. Harris, M. Horton, A. Albert (LAS); G. Shakarji (DMB); clinical chemists and others in the U.S.A., Europe, and Japan. Application of variance component, time series and other analyses to description of reference distributions of clinical laboratory tests, to serial studies of blood chemistries in health and disease, and to the design of criteria for recommended precision and accuracy of laboratory methods. A comparative study of the sensitivity and specificity of univariate and multivariate time series models, using real and simulated data, is nearing completion. A chapter on statistical aspects of reference values in clinical pathology has been published. New research has begun on statistical methods for dynamic assessment of risk in acute illness.

Computer-based studies in ultrasonography. R. Burgess, M. Douglas, J. Bailey, E. Pottala (LAS); B. Maron. Ultrasonography allows non-invasive visualization of many organs without the hazard of ionizing radiation. This project involves development of minicomputer systems for image enhancement, pattern recognition, and three-dimensional reconstruction from ultrasound data sources, principally wide-angle phased array echocardiography. Bone structures opaque to sound necessitate development of an esophageal transducer interfaced to a minicomputer. Lack of staff time during FY81 forced deferral of this effort until FY82.

Mathematical Modeling of biological processes. J. Fletcher (LAS); R. Schubert (Louisiana Tech. University). Development and application of mathematical models in studies of substrate transport in the microcirculation, in diffusion processes in physiology, and in macromolecule-ligand binding equilibria. A theoretical reanalysis of concurrent flow models for organ perfusion experiments has been completed. Modeling and experimental work on microcirculatory processes in the autoregulation of oxygen supply within an organ is continuing.

Mechanisms of active transport/biochemical

kinetics. B. Bunow (LAS); A. Kaplan (NCI); D. Mikulecky (Medical College of Virginia; J. Kernevez (University of Tech., Compiègne, France).

Experimental and mathematical studies of the energy mechanisms for active transport and of multi-state biochemical kinetics in cells and membranes.

Theoretical studies last year revealed the insufficiency of current, widely accepted methods and hypotheses to explain the energizing or localizing of active transport mechanisms.

Collaborative work with NIH scientists has begun on the use of newly implemented network simulation programs to improve the understanding of active transport mechanisms in membranes.

Hybrid computing to analyze physiologic signals and construct simulation models.

E. Pottala, J. Wolpert (LAS); various NIH and FDA scientists.

Using LAS minicomputer system (MAC-16) for hardware simulation of physiologic functions and for analysis of analog signals (myogram, EEG, etc.). An operating system developed and implemented last year has been used extensively for A/D conversion and spectral density analysis of EEG's and EMG's of patients in various studies with the Medical Neurology Branch, NINCDS, and of ECG's in a cardiac drug toxicity study sponsored by the FDA.

Image processing in electron-loss spectroscopy.

M. Douglas, E. Pottala (LAS); J. Costa (NIMH); Development and implementation of mathematical models and image enhancement techniques to analyze computer-acquired information from electron-loss and X-ray spectra indicating the location of extremely small quantities of important chemical elements and active protein molecules within cells. Image processing capabilities developed on the newly expanded DeAnza system have been used to determine fluorine distributions within the dense bodies of blood platelets as a possible model for intracellular patient monitoring of therapeutic drugs.

Mathematical and computational methods for

nonlinear equations. R. Shrager, R. Hendler (NHLBI); A. Schechter (NIADDK). Study of methods of fitting nonlinear models and mathematical methods of spectral analysis. A decomposition procedure for the analysis of the spectra of mixtures of chemical reactants to determine individual physico-chemical characteristics and reactive mechanisms has been completed and is being tested in several experimental applications.

SPONSORING SERVICE (or AGENCY CONTRACT NUMBER)	U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE	PROJECT NUMBER
PROJECT NUMBER (or REF. NO. AND DATE)	PHYSIOLOGIC SCIENCES CENTER	201 CT00007-13 LAS
INTERNAL RESEARCH PROJECT		
PERIOD COVERED October 1, 1980 to September 30, 1981		
TITLE OF PROJECT (in characters or less) Statistical Research in Clinical Pathology		
NAMES, LABORATORY AND INCLUDES AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: E.K. Harris Chief, Lab. of Applied Studies LAS DCRT OTHERS: A. Albert Fogarty International Research Fellow (Sedgum) LAS DCRT G. Shukarg Supv. Systems Analyst DMB DCRT M.S. Horton Computer Systems Analyst LAS DCRT L.W. Horton Research Mathematician LSN DCRT R. Elin Clinical Pathology CC G.Z. Williams Institute for Health T. Yatsaka San Francisco, CA R. Medical Service Dept. G. Siest and Osaka, Japan R. Gueyone Centre du Medicament Preventive, Nancy, France		
COORDINATING UNIT(S) (1-4 max.)		
LABORATORY		
SECTION		
INSTITUTE AND LOCATION		
FUNDING AGENCY		
TOTAL AMOUNT		
FUNDING AGENCY (1-4 max.)		
[] (a) NON-RESEARCH [] (b) HUMAN RESOURCES [] (c) OTHER		
[] (a) MEDICAL [] (b) NUTRITION		
SUMMARY OF WORK (200 words or less - underline key words)		
Univariate and multivariate time series models and discriminant techniques are being applied to various data bases consisting of short series of measurements of serum biochemistry in healthy subjects and patients with myocardial infarction. The purpose is to gain practical experience in the use of these statistical predictive techniques to detect changes and trends within individuals, taking into account biological variation and measurement error. The time scale of these series varies from daily to weekly, 6-month, and 12-month intervals between observations. Parallel computer-based simulation studies are also underway, particularly to estimate the relative sensitivities and specificities of multivariate and univariate forecasting methods. Mathematical investigation into the properties of a new stochastic model of linear change are continuing.		
PROJECTED (Rev. 10-76)		

Numerical methods for the solution of mathematical models describing reaction-diffusion and other processes in biological systems. M. Bieterman, J. Fletcher, B. Bunow (LAS); I. Babuska (University of Maryland). Study, development, and implementation of efficient, flexible numerical methods for the solution of nonlinear ordinary and partial differential equations involved in modeling dynamic physiological processes. Research and testing continued during FY82 on the use of finite element numerical methods for the solution of time-dependent reaction-diffusion equations. Mathematical theory has been developed for the adaptive solution of coupled systems of kinetic equations. Applications to laser light scattering in gels and some hydrodynamic models of blood flow are currently in progress.

Research Projects

Statistical Research in Clinical Pathology

Univariate and multivariate time series models and discriminant techniques are being applied to various data bases consisting of short series of measurements of serum biochemistries in healthy subjects and patients with myocardial infarction. The purpose is to gain practical experience in the use of these statistical predictive techniques to detect changes and trends within individuals, taking into account biological variation and measurement error. The time scale of these series varies from daily to weekly, 6-month, and 12-month intervals between observations. Parallel computer-based simulation studies are also underway, particularly to estimate the relative sensitivities and specificities of multivariate and univariate forecasting methods. Mathematical investigations into the properties of a new stochastic model of linear change are continuing.

Objectives: To investigate applications of statistical theory, particularly the use of variance components, discriminant analysis, and the theory of discrete and continuous time series, to the interpretation of serial clinical laboratory measurements in healthy subjects and patients with acute and chronic disease.

Recent Background: During the past several years, the major effort in this project has been devoted to the application of recently developed mathematical-statistical models to various data bases of serial biochemistries in healthy subjects. The smallest of these data collections, weekly measurements of 10 common constituents in 37 male volunteers over a 5-month period, arose from a cooperatively designed study with the Clinical Research Centre, Harrow,

England. Larger studies, in San Francisco and in Osaka, Japan, involve hundreds of men and women undergoing annual or semi-annual examination including clinical chemistry and hematology measurements. Running parallel with these studies has been a rapidly growing interest among many clinical laboratory workers and clinicians in the statistical bases of reference values commonly used in diagnosis and the evaluation of therapy. In particular, the need to take account of within-person biological variability over time is becoming more widely recognized among pathologists and others who interpret clinical laboratory reports.

Progress during FY81: The application of multivariate and univariate time series models to selected groups of semi-annual measurements from a large-scale health maintenance program in Japan made considerable progress. A preliminary report was presented at an international meeting on the subject of automated health testing in Tokyo, October 1980. Current findings, based on both these and computer-generated observations, indicate that multivariate subject-specific reference regions, like their counterparts derived from cross-sectional population-based data, are much more conservative in their interpretation of clinical laboratory results than are univariate reference ranges. At the same time, the multivariate region will occasionally show sensitivity to a combination of results, each of which appears normal when tested separately. Work is continuing to implement and test the multivariate random walk model, whose application to short series is much more difficult than the stationary homeostatic model.

Mathematical study continues of the univariate stochastic linear growth model able to detect true changes in slope, free of effects of measurement errors and random 'ups and downs.' In cooperation with the Laboratory of Statistical and Mathematical Methodology, research into the asymptotic properties of this model has been completed and efforts have been directed towards obtaining more efficient estimates of the parameters than are now available from current methods based on the variances of second and third differences.

In a new area of research, methods involving discretized response curves are being developed to deal with rapidly changing biochemical variables, as in patients under intensive care for myocardial infarction. The object here is to discriminate as early as possible the probable outcome of the patient's condition using only the most appropriate measurements at each stage.

Studies with collaborating scientists outside NIH on

Mathematical Models of Binding Equilibria

The objective of this project is the study of mathematical models of ligand-receptor or ligand-macromolecule binding studies at equilibrium. The models are examined for mathematical as well as for conceptual validity and are studied to determine their suitability for fitting to experimentally obtained laboratory data. The appropriateness of various model fitting criteria are studied and general guidelines and computational algorithms are designed for computer-aided interactive model fitting.

Background: Mathematical models of macromolecule-ligand binding equilibria have been investigated since 1966. This continuing effort has revised many of the concepts related to the binding of ligands to macromolecules, particularly small ions to proteins. This project has produced an interactive methodology for the fitting of binding models to data and has developed other computer oriented tools for the analysis of data from laboratory experiments.

Progress in FY81: In FY81 numerous requests for copies of exportable computer algorithms were honored and some consultation was provided. Preliminary studies of cooperative binding in Aspartate Transcarbamylase in collaboration with the Clinical Pharmacology Branch of NCI were not experimentally reproducible. Activity in this area has been suspended until the experimental procedure can be improved.

Significance to Biomedical Research: The fitting of models to experimentally obtained data is a procedure used to estimate unknown parameters in mathematical models. The proper choice of a model, a choice of goodness of fit criteria, and the ability to estimate the unknown parameters is a basic need of biomedical research. The estimation of unknown biochemical parameters contributes to new biomedical insight and adds to basic scientific knowledge only if the fitted models represent the underlying biological process and the unknown parameters can be readily and accurately estimated. A thorough and continuing critique of such models and their appropriateness for the interpretation of current laboratory and clinical experiments is therefore essential to the growth of fundamental knowledge in these areas.

The cumulated findings of the previous AMS research in this area has been collected in the form of a summary report. This report details the various alternative models, graphical presentations of data, and algorithms for fitting models to data. Fitting algorithms are also available for fitting with other than the least squares criteria. The development of

these criteria is detailed elsewhere. Publication of this summary report was delayed again due to extensive revision requirements caused by the computer center conversion to the new version of WYLBUR.

Some mathematical considerations of new experimental designs are being explored in collaboration with Dr. Roy of NIADDK. The questions involve the ultrafiltration techniques and the measurement of 8-amino-adenosine binding. The experimental procedures have not yet been validated.

Proposed Course: Applications of existing and new methodology to data analysis will continue to be made as they are requested by collaborating laboratories. Computer programs, reprints and reports continue to be provided to requesting consultees. Publication of the summary report, which was again delayed due to conversion problems in the new version of WYLBUR special train print, is expected in FY82. Analytical development of new models and continued research in this area will emphasize validation of experimental techniques, multi-receptor models, and conformational changes in macromolecules due to binding of ions.

Publications and Abstracts: none

Mathematical Modeling of Substrate Transport in Physiological Environments

Mathematical models of microcirculatory structure and function are developed from conceptual models into systems of coupled ordinary and/or partial differential equations. Methods of solution of these nonclassical formulations are developed and tested and satisfactory cost effective methods are used to explore the properties of these models. The results are interpreted in terms of microcirculatory physiology and are published in the scientific literature.

One objective of this project is to study whole organ and organ tissue level phenomena by means of mathematical models in an effort to determine relationships between variables that govern the organ response to physiologic challenges.

Background and Objectives: The objectives of this project are to develop mathematical models that can be used to simulate microcirculatory physiology and to explain, interpret and/or predict physiologic behavior and limits. Such models should lead to a better understanding of the biological control processes and should suggest improved clinical approaches to microcirculatory disorders.

DATE: OCT 1, 1980 TIME: 10:00 AM ANALYSIS OF COUPLED TRANSPORT AND BIOCHEMICAL KINETICS		PROJECT: CT 070033-05 LAS
TITLE: ANALYSIS OF COUPLED TRANSPORT AND BIOCHEMICAL KINETICS		
PI	B. Bunow, Dr.	Expert LAS DORT
OTHERS:	J. Kornevez, Dr.	Professor Univ. of Tech. Compiègne, France
	A. Kaplan, Dr.	Research Biochemist DCCP-NCI
	D. Maslucky, Dr.	Professor Medical College of Virginia
FUNDING AGENCY: None		
ADDRESS: Laboratory of Applied Studies		
APPLIED MATHEMATICS SECTION		
TITLE: ANALYSIS OF COUPLED TRANSPORT AND BIOCHEMICAL KINETICS		
DATE: 10/1/80	TIME: 10:00 AM	PROJECT: CT 070033-05 LAS
ANALYSIS OF COUPLED TRANSPORT AND BIOCHEMICAL KINETICS		
This project investigates three fundamental problems in biology: (1) the role of dynamic patterns in embryology and evolution, (2) the kinetics of enzymes located in cell membranes, and (3) the kinetics of enzymes from malignant and normal cells in culture. The first area involves investigation of the role which simultaneous reaction and diffusion might play in the spatial and temporal organization of organ shapes and surface markings, as well as oscillatory behavior. The second area involves investigation of molecular mechanism solely from gross observation. The third area involves the integration of instrumentation for data acquisition, display, and transmission, as well as mathematical analysis of kinetic studies on lactate dehydrogenase, an enzyme whose function and molecular form is altered in hepatocytes in tissue culture subject to chemical transformation to a malignant state. Digital computer simulation, particularly by means of network modeling languages, numerical solution of differential equations, and nonlinear regression analysis are the main tools in these investigations.		

The mathematical modeling of organ substrate supply by the microcirculation has been under study since FY69. The substrate of primary interest is oxygen. Such modeling studies are aimed at the prediction of threshold and critical limits of substrate supply necessary to sustain cell function under a variety of physiologic conditions. The responses of models to varying blood flow, blood hemoglobin characteristics, tissue metabolic rate, tissue binding proteins, and other physiologic parameters have been examined. The complex interaction of microcirculatory geometry, nonlinear oxygen hemoglobin dissociation properties, intracellular binding proteins, and substrate dependent metabolic rates requires a detailed description to achieve physiologic validity. These models require the mathematical and numerical computer solution of a system of coupled equations from a distributed parameter model which are of an unusual nonlinear type. The objective of the computations is to identify mathematical models of organ microcirculation having characteristics that correlate with experimentally obtained measurements. Such models can then be used to examine probable organ response to physiologic challenge.

Significance to Biomedical Research: Such modeling is necessary to predict the state of local tissue conditions since direct measurements are generally not possible and must be inferred from boundary observations. Studies of this type have the potential of predicting tissue oxygenation and reoxygenation in ischemia, hypoxia, anemia, coronary obstructions, sickle cell anemia, shock, and other conditions of substrate normal and abnormal physiology.

Mathematical models offer the only technique available for the quantitative study of possible autoregulatory mechanisms. The qualitative and quantitative nature of such mechanisms can be explored by means of appropriate models.

Proposed Course: It is anticipated that the research course of this project will have the following stages.

- Reexamine the Krogh cylinder model and its adequacy for the representation of perfused organ microcirculation.
- Develop exact mathematical solutions for the Krogh model that exhibit tissue axial diffusion and capillary axial diffusion for the steady state constant metabolic rate experiments with perfused organs.
- Develop or modify numerical algorithms that will compute substrate levels for nonconstant metabolic rates and other nonlinear effects.
- Develop algorithms for the direct comparison of distributed substrate level computations with

experimentally obtained micro-electrode measurements.

(e) Identify those critical ranges of parameters that control organ response to physiologic challenge.

Progress in FY81: During FY81 attempts were made to use mathematical solutions in the existing literature to validate an experimental design for perfused organ studies. The numerical results revealed that these solutions, for the cell-free perfused Krogh cylinder model, were mathematically incorrect. Our efforts were subsequently redirected to the development of new, intricate, mathematically correct, solutions of the Krogh cylinder model. The analytical construction and examination of these mathematical solutions is being completed, and these solutions are being explored parametrically for critical ranges and limits. Two preliminary reports on these properties have been presented at international meetings, and a detailed theoretical publication has been submitted.

The following stages of the proposed course have been accomplished.

(a) Reexamine the Krogh cylinder model and its adequacy for the representation of perfused organ microcirculation.

(b) Develop exact mathematical solutions for the Krogh model that exhibit tissue axial diffusion and capillary axial diffusion for the steady state constant metabolic rate experiments with perfused organs.

Publications and Abstracts:

- Fletcher, J.E.: Simulation: Procedures and Pitfalls. *Proceedings of the 34th ACEMB meeting*, Houston, Texas, 1981 (abstract).
- Fletcher, J.E., and Jolly, M.: The Computation of Substrate Levels in Perfused Tissues. *Proceedings of the Annual Siam Meeting*, Houston, Texas, 1980 (abstract).
- Fletcher, J.E., and Schubert, R.W.: Substrate Level Prediction and Histograms in Perfused Tissues. *Proceedings of the 34th ACEMB meeting*, Houston, Texas, October 1981 (abstract).
- Fletcher, J.E., and Schubert, R.W.: The Theoretical Prediction of Substrate Levels and Their Histograms in Cell Free Perfused Tissues. *Proceedings of the International Meeting of OTT Society*, Detroit, Michigan, August 1981, Plenum Press (in press).

Analysis of Coupled Transport and Biochemical Kinetics

This project investigates three fundamental in biology: (1) the role of dynamic patterns in embryology, (2) the kinetics of enzymes in cell membranes, and (3) the kinetics of enzymes from malignant and normal cells. The first area involves the role which simultaneous reaction and diffusion might play in the spatial and temporal organization of organ shapes and surface markings. The second area involves enzyme kinetics with special emphasis on limitations in inferring molecular mechanism solely from gross observations. The third area involves the integration of instrumentation for data acquisition, display, transmission, and mathematical analysis of kinetic studies on lactate dehydrogenase, an enzyme whose function is altered in hepatocytes a malignant state. Digital computer simulation, particularly by means of network modeling languages, numerical solution of differential equations, and nonlinear regression analysis are the main tools in these investigations.

• Dynamic Patterns

Background and Objectives: Temporal and spatial organization is universal in living organisms. What are the mechanisms which produce it? The equations describing diffusion of chemically reacting molecules possess solutions which spontaneously develop spatial and temporal patterns of concentration. Because reaction and molecular motion are the predominant physico-chemical processes of living organisms, it is tempting to suppose that the one is the mechanism of the other. The objectives of this project are to develop numerical methods to solve reaction-diffusion equations so as to investigate the principles controlling pattern formation.

Progress in FY81: The bifurcation diagram of a reaction-diffusion equation summarizes the multiplicity and stability of solutions. This year the bifurcation diagram for the model equations developed previously was successfully computed. Techniques from functional analysis have been applied to determine the multiplicity of solutions. One technical manuscript, long in press, has appeared. A popular presentation is in press, and another popularization has been solicited. The technique for computing bifurcation diagrams has appeared as an internal report at a collaborating institution and will shortly be submitted for publication.

Significance to Biomedical Research: Patterns generated by reaction and diffusion have been hypothesized to play a role in a variety of developmental processes in biology. The validity of

these hypotheses has never been critically tested. Several critical questions about such patterns are addressed: What is the relation between pattern form and the shape of the medium in which the pattern grows? Is there a relation between the patterns seen and the molecular mechanism of the reaction? Are the patterns unique and stable?

Future Course: A formalism for dealing with bifurcation to temporally periodic solutions has been acquired. During FY82 this theory will be used to direct experimental research into spatially distributed oscillations in a membrane containing the immobilized enzyme phosphofructokinase.

- Kinetics of Enzymes in Membranes

Background and Objectives: Studies of the mechanism of membrane transport and excitable membranes are generally less precise than studies of the mechanisms of enzymes in solution. This uncertainty arises because it is difficult to manipulate the environment of the interior of a biological membrane and also difficult to measure responses there. There are two objectives to this project: to determine the extent to which the actual organization of models for membrane-associated processes can be correctly inferred from the kinds of experimental measurements currently made, and to develop a formalism within which complex kinetics can be entered rapidly and accurately as data into a simulation program.

Progress in FY81: During FY81 the network simulation languages SPICE and NET-2 were installed on the IBM 370 central computers. Several collaborative projects have shown the utility of these languages for rapidly building and testing models for a variety of biological phenomena. In the area of membrane transport, SPICE modeling of several molecularly distinct schemes showed them to be experimentally indistinguishable. This material was presented at the Polish Winter School of Membrane Transport and has been submitted for publication. To demonstrate the utility of network modeling to the NIH community, a course is conducted through DCRT; this year a dozen investigators attended. A book on the application of network methods to physiological simulation is in preparation, as is a manuscript on use of network methods for physiological models based upon partial differential equations. Examples from the areas of microcirculation and axon physiology are illustrated. Recently, a second type of network, called a state transition network, has been employed successfully in the characterization of several types of membrane processes. The means of translating such networks into SPICE, gaining considerably in the size and

generality of models that can be considered, has been demonstrated. An invited illustrative paper was delivered at a recent conference on NET-2 conducted by the Navy.

Significance for Biomedical Research: The choice of a model for a biological process strongly conditions the design of experiments to confirm and extend it. By making the analysis of models sufficiently simple, an investigator is given the freedom to consider many models. From comparisons among the models using simulation, it should be possible to develop incisive experiments which permit scientifically valid, rather than arbitrary, selection among the models. The network languages nicely complement the MLAB system in permitting users to model phenomena too complex to be conveniently described in MLAB.

Future Course: During FY82, an effort will continue to proselytize the NIH community on the utility of network modeling. A compendium of transition state networks, currently in preparation, will provide the basis for development of the concept of distinguishable classes of models in a number of areas of membrane biology. The extent to which current experimental techniques actually provide confirming data for the models which they employ can then be determined.

- Kinetics of Lactate Dehydrogenase(LDH) from Normal and Malignant Hepatocytes

Background and Objectives: When the enzyme LDH is isolated from normal and malignant hepatocytes grown in tissue culture, there are differences both in the activity of the enzyme and its sensitivity to inhibition by a reaction product. The objective of this project is to characterize the differences in LDH from various sources, emphasizing particularly the differences between normal and transformed cells.

Progress in FY81: The method of kinetic analysis was applied to LDH obtained from several sources, including normal and transformed hepatocytes. Differences detected in this way were also reflected in iso-electric focusing studies on the enzyme from the two sources. The apparatus for performing the kinetic studies was installed at NIH. A microcomputer was purchased and installed by the principal investigator that permits data from stopped-flow spectrophotometry of LDH kinetics to be stored, edited, and transferred to NIH computers for further analysis. Software for this purpose has been acquired. A manuscript describing the work is about to be submitted.

Significance to Biomedical Research Differences in the enzyme not evident from other types of analysis

can be shown through kinetic studies. The method of kinetic analysis employed here distinguishes between LDH from normal and chemically transformed hepatocytes, whereas the enzymes from these two sources are indistinguishable by isozyme analysis. The technique is probably applicable to LDH from other organ sources, although this remains to be shown.

Future Course: During FY82 the new computer will be employed to extend this type of analysis to cells from other types of malignancies.

Publications:

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- Sharan, M., Kernevez, J.P., and Bunow, B.: On numerical exploration of bifurcating branches of solutions in reaction diffusion equations modeling enzymatically active artificial membranes. *Research report of the Department of Applied Mathematics*. University of Technology of Compiègne, Compiègne, France, 50 pp.

PI NAME & ADDRESS NOV 1981	DEPARTMENT OF MATHEMATICS UNIVERSITY OF MARYLAND COLLEGE PARK, MD 20742	PROJECT NUMBER Z01 CF00010-05 LAS
October 1, 1980 to September 30, 1981 Title of Project (50 characters or less) Nonlinear Equations		
NAMES, LABORATION AND UNIVERSITY AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: R.L. Chirager Mathematician LAS DCRT OTHERS: G.H. Knott Computer Specialist LAS DCRT J.F. Fletcher Chief, AMS LAS DCRT T.A. Hunter Biostatistician LFR INHUBI A. Schechter Physician LFR NIADDK		
COOPERATING UNITS (1 to 4) NONE		
LAB/BRANCH Laboratory of Applied Studies SECTION Applied Mathematics Section INSTITUTION AND LOCATION NCW, NIH, Bethesda, MD 20205 TOTAL MANPOWER: PROFESSIONALLY 1.0 OTHER 0.0 CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEUTRIN <input checked="" type="checkbox"/> (a) MINDS <input type="checkbox"/> (a) INTERVIEWS SUMMARY OF WORK (100 words or less - underline headings) Methods are developed for solving nonlinear equations frequently encountered in mathematical modeling at NIH, usually in the context of constrained nonlinear least squares or in the solution to nonlinear differential equations. Related problems, such as asymptotic error analysis and the efficient treatment of sparse systems, are also considered.		
PROJECT (See 10-11)		

PI NAME & ADDRESS NOV 1981	DEPARTMENT OF MATHEMATICS UNIVERSITY OF MARYLAND COLLEGE PARK, MD 20742	PROJECT NUMBER Z01 CF00010-03 LAS
October 1, 1980 to September 30, 1981 Title of Project (50 characters or less) Numerical Approximation Techniques for the Solution of Reaction-Diffusion Systems in Biology		
NAMES, LABORATION AND UNIVERSITY AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: M. Bieterman Mathematician, AMS LAS DCRT OTHER: J.F. Fletcher Chief, AMS LAS DCRT B. Runow Biostatistician, AMS LAS DCRT I. Habskja Professor, Institute of Physical Univ. of Md. Science and Technology		
COOPERATING UNITS (1 to 4) NONE		
LAB/BRANCH Laboratory of Applied Studies SECTION Applied Mathematics Section INSTITUTION AND LOCATION NCW, NIH, Bethesda, MD 20205 TOTAL MANPOWER: PROFESSIONALLY 0.0 OTHER 0.0 CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEUTRIN <input checked="" type="checkbox"/> (a) MINDS <input type="checkbox"/> (a) INTERVIEWS SUMMARY OF WORK (100 words or less - underline headings) The use of mathematical models to describe reaction-diffusion systems and other biological processes requires the implementation of reliable, computationally efficient algorithms for the computer solution of nonlinearly coupled partial differential equations. New numerical approximation techniques are studied and related software is developed for the solution of model reaction-diffusion systems. Existing methods and previously written programs are altered and applied to other biological problems.		
PROJECT (See 10-11)		

Nonlinear Equations

Methods are developed for solving nonlinear equations frequently encountered in mathematical modeling at NIH, usually in the context of constrained nonlinear least squares or in the solution to nonlinear differential equations. Related problems, such as asymptotic error analysis and the efficient treatment of sparse systems, are also considered.

Background and Objectives: The objective of the project is to develop methods for solving the nonlinear equations frequently encountered in descriptions of biomedical problems at NIH. General categories of problems for which solutions were developed here (partially or wholly) are nonlinear least squares with linear constraints, nonstiff and stiff ordinary differential equations, and nonlinear curve fitting in norms other than least squares. In addition, every project with which this one interfaces (i.e., collaborations) presents its own set of special equations which must be solved, in either the analytic or numerical sense. Methods which prove to be of general utility are developed into accessible computer programs or routines, e.g., MODELAIDE and MLAB.

Progress in FY81:

• MLAB Projects

Gary Knott, (DCRT). The root-finder has been revised with considerable improvement in efficiency and the techniques are being described in a manuscript in progress. An extension of the curve-fitter is being considered which could include not only least-pth power fits (added this year) but also maximum likelihood and M-estimation in which the likelihood function itself may contain parameters. The approach thus far has been to use the current Levenberg-Marquardt algorithm but alter the manner in which the function to be fit is presented to the algorithm.

• GABA Metabolism

E. Anthony Jones, Dan Schafer, Peter Ferenci, (NIADDK). GABA is a neurotransmitter which is stored only in brain cells. In normal animals, GABA concentration is higher in plasma than it is in cerebro-spinal fluid, and higher still in the portal vein. Recent experiments indicate that gut bacteria produce GABA which is then mostly degraded in the liver. When the liver fails, the blood-brain barrier breaks down, and the role of GABA in this process is not well understood. Data is now being processed on the metabolism of 3H-GABA from normal rabbits and rabbits in liver failure to determine the resulting alteration in GABA metabolism. Other experiments

(e.g., impairment of GABA metabolism without liver failure) will follow.

- **Equilibrium Studies of Magnesium Phosphate**
Lev Jacobson (NIADDK). The physiologically important reactions between Mg and PO₄ are not well understood. Various models are being applied to the fitting of NMR and pH data, with considerable improvement in data expected when a divalent metal electrode is used to detect magnesium ions.

- **Analysis of Experimental Spectra**
R.W. Hendler, D.Y. Setty, Dan Robertson (NHLBI). A paper on the use of singular value decomposition (SVD) in data matrices to detect chemical transitions and their associated spectra is in the final stages of revision. New data from beef heart mitochondria indicate that cytochromes in mammalian cells have essentially the same mechanism for passing electrons as that observed in the bacteria. Spectra to verify this will soon be forthcoming for processing by SVD or a related method. A paper on oxygen uptake and proton release by cells and reconstituted vesicles has been submitted.

- **Phytic Acid Titration.**
William Evans (Dept. of Agriculture, New Orleans). Phytic acid is a chelating agent which may be a factor in metal-deficiency diseases. A manuscript, on the liganding mechanism, has been revised and resubmitted to *The Journal of Agriculture and Food Chemistry*.

- **Hemoglobin production**
A.N. Schechter, Ann Dean, Francois Erard (NIADDK). An abnormal human cell line, called k562 cells, can be induced by addition of hemin to produce embryonic and fetal hemoglobins. Inhibitors of cell division cause these cells to accumulate hemoglobin, and the combined effect is a hundred-fold increase in Hb concentration. Can all the effects observed be explained by a simple kinetic model in which only hemin controls production rates? The data are now being processed.

Significance to Biomedical Research: These methods are essential for the resolution of problems of data analysis in metabolism, cell growth, chemical kinetics, and spectral analysis (UV, IR, CD, ORD, NMR, ESR).

Proposed Course: The new root-finder will be compared with the current techniques in the existing literature and the results will be published. The maximum-likelihood and M-estimation curve-fitter will be developed and tested. If it proves feasible, the syntax of MLAB will be modified to permit easy use. The new data from beef-heart mitochondria will be processed by the SVD technique. Simultaneous

measurements from pH and divalent-metal electrodes are expected to clarify the modeling of the magnesium phosphate system.

Publications and Abstracts:

Berk, P.D., Blaschke, T.F., Shrager, R.I., Waggoner, J.G. Phenobarbital does not increase hepatic turnover in Man *Gastroenterology* 79 1004, 1980

Numerical Approximation Techniques for the Solution of Reaction Diffusion Systems in Biology

The use of mathematical models to describe reaction-diffusion systems and other biological processes requires the implementation of reliable, computationally efficient algorithms for the computer solution of nonlinearly coupled partial differential equations. New numerical approximation techniques are studied and related software is developed for the solution of model reaction-diffusion systems. Existing methods and previously written programs are altered and applied to other biological problems.

Background and Objectives: Mathematical models describing many biological and physicochemical processes involve systems of coupled ordinary and partial differential equations that first must be formulated and then solved via computer. It often happens that the necessary numerical algorithms do not exist in the literature, the related computer programs are unavailable, or that applicable software requires a large amount of computer time, rendering its implementation impractical. The two objectives of this project are the development of new, efficient numerical techniques for the solution of equations describing reaction and diffusion processes and the modification and implementation of existing programs to solve other specific biological problems.

Progress in FY81 The investigation of an adaptive 'method of lines' solution approach and the implementation of known techniques for the approximate numerical solution of time-dependent partial differential equation systems arising in biology have continued in FY81.

Significance to Biomedical Research: A variety of reaction, diffusion, and transport processes occurring in biomedical application areas are modeled by equations which can be solved by the techniques being developed. Among these processes are oxygen transport in the microcirculation, embryologic pattern formation, nerve impulse transmission, and population dynamics of ecological systems. Effective modeling of such nonlinear distributed parameter systems involving both reaction and diffusion requires the use of accurate, computationally

PROJECT TITLE: LAS INFORMATION PROGRAM	PROJECT NUMBER: Z01 CT00034-05 LAS
PROJECT START DATE: October 1, 1980 to September 30, 1981	
PROJECT DESCRIPTION: Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease	
PROJECT FUNDING SOURCE: LAS	
PROJECT PI: R. C. Burgess, Senior Staff Fellow, LAS DCRT	
A. W. Nussbaum, Chief, CMB NHLBI, LAS DCRT	
J. J. Bailey, Chief, MAS, LAS DCRT	
R. G. Crystal, Chief, PB NHLBI, LAS DCRT	
OTHERS: E. R. Harris, Chief, LAS DCRT	
M. R. Horton, Computer Systems Analyst, LAS DCRT	
E. W. Pottala, Electronics Engineer, LAS DCRT	
PROJECT LOCATION: Clinical Hematology, Pulmonary Branch, NHLBI, Nuclear Medicine Dept., CC Branch, NHLBI	
PROJECT ORGANIZATION: Laboratory of Applied Studies	
APPLIED MATHEMATICS SECTION, MEDICAL APPLICATIONS SECTION	
PROJECT START DATE: OCT 1, 1980	
PROJECT END DATE: SEP 30, 1981	
PROJECT FUNDING SOURCE: LAS	
PROJECT PI: R. C. Burgess	
OTHERS: A. W. Nussbaum, J. J. Bailey, R. G. Crystal, E. R. Harris, M. R. Horton, E. W. Pottala	
PROJECT DESCRIPTION: This project--through a collaborative effort of LAS with the Nuclear Medicine Department, CC and the Clinical Hematology and Pulmonary Branches, NHLBI--is directed toward a deeper understanding of pulmonary pathophysiology through the construction of computer-based models of pulmonary gas exchange and respiratory mechanics and comparisons of model predictions with real patient data.	

efficient numerical algorithms. These methods and other standard techniques are available to the NIH biomedical community as research tools and can be modified or used directly to solve problems of physiologic interest.

In the 'method of lines' approach the finite element technique is used to approximate the spatial variables. This yields a system of ordinary differential equations which can be solved, for example, by one of the many high quality software packages available. The scheme is adaptive in that decisions concerning mesh selection and refinement are made by the computer during the problem solution. Such decisions are based upon reliable a posteriori estimates of the error between the exact solution and the computed approximate solution. Changes in the mesh structure are made in order to control the error and increase the efficiency of the solution process. Such schemes are especially applicable to dynamic biological systems whose behavior is localized in space.

Work has been completed which extends the full mathematical framework of the a posteriori error analysis developed for single, steady-state equations by I. Babuska and W. Rheinboldt to coupled, time-dependent linear systems of partial differential equations. Adaptive mesh selection strategies based upon these estimates have been developed and are being implemented in computer programs on the NIH IBM System 370. The accuracy and efficiency of the adaptive procedure are to be tested on a collection of nonlinear problems of biological interest.

In addition to the above investigation, recent collaborative efforts have been initiated with two NIH researchers:

1. A preliminary study with Dr. Robert Lutz, DRS/BEI, has been completed. The study examined the solution of the Navier-Stokes equations for a two-dimensional model of blood flow through a section of an inelastic canine aorta model. This collaboration will involve implementing a fluid dynamics finite element code, which will either be obtained and modified, or designed and written by LAS. Computed wall shear stresses and blood velocity profiles are to be compared to laboratory experimental data and used in a parametric study of factors relevant to the onset of atherosclerosis.

2. Work with Dr. Ralph Nossal of DCRT/PSL is underway to determine if modified versions of the Bathe-Wilson finite element code could prove useful in deducing the elastic properties of gels from light scattering measurements. In a mechanically excited gel, the frequencies of standing waves are related to the elastic properties of the gel. In most

experiments, these frequencies can be only approximated crudely. The objective here is to develop a scheme for approximating these frequencies by a finite element technique.

These collaborative projects will continue at levels determined by LAS/AMS priorities and manpower.

Publications and Abstracts: None

Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease

This project—through a collaborative effort of LAS with the Nuclear Medicine Department, CC and the Clinical Hematology and Pulmonary Branches, NHLBI—is directed toward a deeper understanding of pulmonary pathophysiology through the construction of computer-based models of pulmonary gas exchange and respiratory mechanics and comparisons of model predictions with real patient data.

Background and Objectives: Numerous attempts have been made in the past to quantify pulmonary function. Inhomogeneities in the lung required certain simplifying assumptions to be made tending to obscure the true nature of lung function. Furthermore, certain nonlinearities inherent in the lung system allowed only partial quantitative models and sometimes these could only be expressed in the form of nomograms or graphs.

Within recent years it has been possible to apply computer technology to numerous diagnostic tools, viz, spirometry, dynamic compliance studies, multiple inert gas studies, pulmonary scintigraphy, cardiac catheter studies, and blood gas studies.

The objectives of this program include the use of computer technology to refine diagnostic methods and to construct models for pulmonary gas exchange and respiratory mechanics.

Progress in FY81: The existing system for analysis of gas exchange was tested extensively. It was found that instabilities in the gas analysis lines and in the analog circuitry prevented any hope of obtaining reliable data. Therefore, the system was completely re-designed. Literature on exercise-testing laboratories was reviewed; the state-of-the-art in commercial equipment was analyzed; and one of the most advanced exercise-testing laboratories (Wasserman in California) was visited. LAS developed specifications and directed purchase of the equipment, much of which has been delivered. The basic components of the new system include: an LSI-11 based computer for rapid data acquisition and processing; a pneumotachometer and mass spectrometer to provide flow and concentration data;

and a bicycle ergometer and treadmill whose work loads can be varied under direct computer control.

Significance: In certain diseases of the lungs (restrictive, obstructive, etc.), blood (hemoglobinopathy sickle cell anemia, polycythemia), and cardiovascular system, the assessment of the patient's condition at various points in the course of disease may be no better than a subjective impression given by the patient, his family, or his physician. An alternative, and potentially more objective, method of assessment involves the use of continuous exercise to quantitatively evaluate the overall ability of the patient to meet the demands of exercise. This is accomplished by monitoring his ECG, blood pressure, blood gases and lactate, oxygen consumption, etc., in a reliable and reproducible manner. The detection of 'anaerobic threshold' may be of particular clinical importance when considering response to therapy or disease progression.

The sensation of 'shortness of breath' is poorly understood. This phenomenon clearly has components of neural as well as clinical origin. Non-steady state exercise measurements should give additional insight into the origin of this complaint in patients with various disease processes. This data, in conjunction with other parameters, should improve prognostic accuracy and aid the therapeutic decision-making process.

Proposed Course: Configuration and interfacing of the system is in progress and will continue into FY82. Many components from the old system (e.g., bicycle ergometer, Tektronix display) will be incorporated. When assembled, the new configuration will be tested extensively for reliability. Subsequently, a normal data base using volunteers will be acquired as a baseline against which the tests in pathological conditions can be compared.

Publications: None

Proposed Course: No new projects involving simulation models are being undertaken at this time. However, the capability remains, should a collaborative project be proposed in the future. For example, the Laboratory of Neurotoxicology, NINCDS, has studied a rat preparation with bipolar electrodes in the sensory cortex and in two layers of the hippocampus. The theta activity generators in the hippocampus produce certain correlated spindling activities in the sensory cortex, varying according to degree of a drug-induced, immobility state. Data already collected will be analyzed, using the MAC-16 system. Whether additional study is needed using a simulation model remains to be investigated.

The MAC-16 system will have continued use for ECG processing from the Framingham Heart Study (see project report on electrocardiography).

Analysis of FDA data on cardiotoxicity has begun and will continue in FY82.

Publications and Abstracts:

Yaar, I., Shapiro, M.B., Mitz, A.R., and Pottala, E.W.: A computer assisted monitoring of muscle fiber conduction in full interference patterns: ALS versus normal subjects. A preliminary report. The American Association of Electromyography and Electrodiagnosis Meeting Philadelphia, Pennsylvania, 1980. *Electroencephol. Clin. Neurophysiol.* 50:245P, 1980 (abstract).

Yaar, I., Shapiro, M.B., Mitz, A.R., and Pottala, E.W.: Introducing a new computer assisted technique for measuring muscle fiber conduction velocity at full interference pattern. American Neurological Association, Boston, Massachusetts, 1980. *Ann. Neurology* 8:124, 1980, and Transactions of the American Neurological Association 1980 (abstract).

Yaar, I., Shapiro, M.B., and Pottala, E.W.: An EEG power spectral analysis of dopaminergic mechanisms in patients with hepatic coma. American Electroencephalographic Society meeting Boston, Massachusetts, 1980. *Electroenceph. Clin. Neurophysiol.* 51:31P, 1981 (abstract).

Computer Systems for Nuclear Medicine

This project involves computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Nuclear Medicine Department of the Clinical Center and collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiology and myocardial perfusion scintigraphy, renal dynamics, and pulmonary ventilation-perfusion relationships.

Background and Objectives: Since FY72, LAS and CSL have collaborated with the Nuclear Medicine Department, CC in the acquisition and development of several minicomputer systems that gather and process data from the scintillation cameras in the Nuclear Medicine Department.

The objective of this program is to continue development of computer-based algorithms, which have already found wide-ranging applications, including: fitting mathematical models; mapping the parameters of such models over time and in different regions of an organ; image processing; interpolation, expansion, and contraction of image arrays; and pattern recognition.

Progress during FY81:

Renal Scintigraphy--Work in FY76 showed a significant enhancement of radionuclide renography by the use of functional maps, and, since FY77, functional maps have come into routine clinical use in the Nuclear Medicine Department. In FY79-80 a pilot study of partial renal artery ligation was carried out on four dogs. The results of this study were reported at the Society of Nuclear Medicine, and a manuscript is now in preparation. In FY81 the techniques of the pilot study were improved in several ways:

- The studies are uniformly performed with I-123 iodohippuran, improving the signal noise ratio about 16-20 fold;
- A radio-transparent table was designed so that positioning of the animal could be carefully controlled;
- Precise positioning of the kidneys under the gamma camera was guided by technetium-99m DPTA given in minute doses; and
- The software has been entirely rewritten to work in conjunction with the current Nuclear Medicine Operating System and to decrease image variability.

Data on nine dogs including renal scintigraphy and

TITLE (DO NOT WRITE IN THESE SPACES) Computer-Aided Analysis of Electrocardiograms		PROJECT NUMBER Z01 CT00002-11 LAS	
DATE OF PROJECT (20 characters or less) October 1, 1980 to September 30, 1981.			
NAME, GRADE AND INSTITUTE AFFILIATIONS, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONS PARTICIPATING IN THE PROJECT PI: D. J. Bailey - Chief, RMS LAS DCRT M. R. Horton - Computer Systems Analyst LAS DCRT			
OTHERS: E. A. Harris - Chief LAS DCRT M. E. Womble - Aeromedical Cybernetics Branch Brooks AFB, Texas P. MacFarlane - Medical Cardiology Glasgow Royal Infirmary Scotland D. Savage - Framingham Heart Study NHLBI S. Allen - Medical Research Analyst CSL DCRT			
SUMMARY (2000 words or less - underline required.) These studies continuing since 1970 have been directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer analysis for analysis of routine electrocardiograms (ECG's). Further studies will involve new methods of feature extraction and design of criteria by computer techniques and their use in epidemiological studies.			
(NAME, GRADE) (DATE, 1981)			

contrast angiography before and after renal artery ligation has been collected. Preliminary results suggest a vast improvement in technique over the pilot study.

Cardiac Scintigraphy--In collaboration with Nuclear Medicine and the Cardiology Branch, LAS has begun investigation of several parameters reflecting mobility of the heart wall including ejection fraction, time-to-end-systole, phase (of a fitted cosine curve), and ratios of areas over/under the time-activity curve of a blood pool scan. Programs have been written to compute these parameters globally or for any of four sectors of the heart image. The test data base includes rest and exercise studies on 40 normal volunteers, 10 patients with chest pain but completely normal cardiac studies (including ECG and coronary angiogram), 10 patients before beginning adriamycin therapy, and 15 patients with coronary disease and known resting apical abnormalities (hypokinesis, akinesis, or dyskinesis). Preliminary results suggest that ejection fraction and phase are the best parameters for separating normal from abnormal cases.

Image Processing Developments--The DECsystem-10 based image processing packages, IMAGE and PSTACK, continue to be expanded and used both for dynamic scintigraphic images and for electron microscopy images.

In the past year, the LAS DeAnza image processing system has undergone rapid expansion. Two major interactive software packages have been developed. The first, PICTUR, currently includes a variety of edge detection and tracking routines and alignment procedures in addition to display and image enhancement options.

The second, MOVIE, is aimed at time varying image sequences. During the past year this package has been enlarged to include generation of flow/volume loops, phase/amplitude maps and a variety of enhanced dynamic display procedures. These two packages are designed to be compatible with one another; transition from the use of one package to the other is invisible to the user. A magnetic tape drive to facilitate data interchange and a disk drive to improve storage capabilities have been purchased and are being interfaced into the system.

Proposed Course:

Renal Scintigraphy--A project planned in FY80 would have allowed the use of renal scintigraphy to study patients with renal vascular hypertension in collaboration with the Hypertension Branch, NHLBI; it is still awaiting FDA approval of I-123 iodohippuran

as a diagnostic agent. Extension of the canine studies with different lesions is under discussion.

Cardiac Scintigraphy--A statistical analysis of the data collected will be pursued, one possible outcome of which might be a discriminant function of ejection fraction and phase to achieve optimal separation of normals from abnormals. Another interesting study will involve those patients with myopathy secondary to adriamycin therapy, using each patient before therapy as his own control. Those patients who have normal contractility at rest but abnormalities upon exercise form another interesting data base.

Image Processing--The DeAnza image processing system is to be expanded from its current 256x256 image size to a 512x480 image. This expansion, together with the new magnetic tape drive and the disk drive, will facilitate study of paired myocardial (Thallium) and blood pool image sequences. Refined edge detection, assessment of wall motion abnormalities and perfusion, and determination of 'absolute' volumes, if possible, are planned.

A model is to be developed to demonstrate the effect of known amounts of additive noise on the detectability of regional wall motion abnormalities.

Publications: None.

Computer-Aided Analysis of Electrocardiograms

These studies continuing since 1970 have been directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer systems for analysis of routine electrocardiograms (ECG's). Further studies will involve new methods of feature extraction and design of criteria by computer techniques and their use in epidemiological studies.

Background and Objectives: This has been extensively described in last year's *Annual Report* (FY80), pages 111-114.

Progress during FY81: A study of 300 ECG's from the Royal Infirmary in Scotland was published (bibliography follows). This study resulted in the comparison of two ECG programs using guidelines and definitions that were developed by LAS. This method of evaluation, when applied to two or more programs, can reveal their relative strength and weaknesses. The reason for a program failure can often be pinpointed to a specific defect in pattern recognition, measurement algorithm, or design of criteria.

In FY80, the Framingham Heart Study proposed longitudinal studies of routine ECG's in that population. In FY81, LAS collected ECG's on 200 subjects, including 100 blacks, and 25 normals repeated 4 times.

Significance: See *Annual Report* (FY80), pages 111-114.

Proposed Course: Testing of ECG programs developed by other organizations was largely completed in FY79. However the development of 12- or 15- lead ECG data acquisition devices and the use of sophisticated feature extraction methods (e.g., Karhunen-Loeve expansion) opens the possibility for further investigation of ECG diagnostic systems.

Meanwhile LAS continues to study the epidemiologic significance of the routine ECG in collaboration with the investigators of the Framingham Heart Study. The ECG correlates of such heart diseases as coronary disease, mitral prolapse, and asymmetric septal hypertrophy in a free-living population are of particular interest.

Studies of statistical variance within and between individuals already begun will extend into FY82. A separate study to test a black population for differences is planned.

Publications and Abstracts:

- Bailey, J.J.: The future of gold standards and computerized electrocardiography. In Tolan, G.D. and Pryor, T.A. (Eds.): *Computerized Interpretation of the ECG V*. New York, Engineering Foundation, 1980, pp 229-233.
- Bailey J.J., Berson, A.S., Jackson, L.K., Miliken, J.A., Stevens, J.M., Tolan, G.D., and Wolf, H.K. Evaluation Methodologies for ECG diagnostic systems. In Bonner, R.E. and Pryor, T.A. (Eds.) *Computerized Interpretation of the ECG VI*. New York, Engineering Foundation, 1981 (in press).
- Bailey, J.J., and Harris, E.K. Evaluation of ECG interpretation: Truth versus beauty. In Tolan, G.D. and Pryor, T.A. (Eds.): *Computerized Interpretation of the ECG V*. New York, Engineering Foundation, 1980, pp 179-182.
- Bailey, J.J., and Horton, M.R.: Type A electrocardiogram data bases: Purpose and development. In Wolf, H.K., and Macfarlane, P.W. (Eds.) *Optimization of Computer-ECG Processing*. New York, North-Holland Publishing Company, 1980, pp. 189-195.
- Macfarlane, P.W., Chen, C.Y., and Bailey, J.J. A comparison of point scoring techniques for the diagnosis of LVH. In Macfarlane, P.W. (Ed.): *New Frontiers in Electrocardiology*. London, Pitman Medical Publ. Co., 1981 (in press).
- Macfarlane, P.W., Melville, D.I., Horton, M.R., and Bailey, J.J.: Comparative evaluation of the IBM (12 lead) and Glasgow Royal Infirmary (3 orthogonal lead) ECG computer programs. *Circulation* 63: 354, 1981.

PROJECT NUMBER (SEE INSTRUCTIONS)	DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE NATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00043-03 LAS
PERIOD COVERED: October 1, 1980 to September 30, 1981 TITLE OF PROJECT (20 characters or less) Computer-based studies in ultrasonography		
NAMES, LABORATORIES AND INSTITUTES AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED IN THE PROJECT		
PI:	L.W. Pottala	LAS DORT
	S.-J. Norton	CB, NHLBI
OTHERS:	M.A. Douglas	LAS DORT
	J.J. Bartley	LAS DORT
COOPERATING UNITS (if any) Cardiology Branch, NHLBI		
LABORATORY Laboratory of Applied Studies MEDICAL APPLICATIONS SECTION INSTITUTES AND CLINICIAN DORT, NIH, Bethesda, MD 20205 TITLE: ANALYSIS 0.4 PROGRESS: 0.2 OTHER: 0.2 CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEUTRON <input type="checkbox"/> (d) X-RAYS <input type="checkbox"/> (e) IONIZING RADIATION NUMBER OF PAGES (200 words or less - underline separate)		
This project involves collaboration of LAS, with the Cardiology Branch, NHLBI. It is directed toward computer-based processing for image enhancement, pattern recognition, and three-dimensional reconstruction from ultrasound data. The principal sources of data are wide-angle, phased array echo-cardiography.		
(Page 1) (Rev. 2-81)		

PROJECT NUMBER (SEE INSTRUCTIONS)	DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE NATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00042-03 LAS
PERIOD COVERED: October 1, 1980 to September 30, 1981 TITLE OF PROJECT (20 characters or less) Computer Based Analysis and Image Processing in Electron Microscopy and X-ray and Electron-Loss Spectroscopy		
NAMES, LABORATORIES AND INSTITUTES AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED IN THE PROJECT		
PI:	M. A. Douglas	Computer Systems Analyst LAS DORT
	J. L. Costa	Medical Officer CN, NIMH
OTHERS:	E. W. Pottala	Elnc. Eng. Chief, MAS CSL DORT
	J. J. Bartley	LAS DORT
COOPERATING UNITS (if any) Clinical Neuropsychology, NIMH, Laboratory of Chemistry, NIAADD		
LABORATORY Laboratory of Applied Studies MEDICAL APPLICATIONS SECTION INSTITUTES AND CLINICIAN DORT, NIH, Bethesda, Maryland 20205 TITLE: ANALYSIS 2.1 PROGRESS: 2.0 OTHER: 0.1 CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEUTRON <input type="checkbox"/> (d) X-RAYS <input type="checkbox"/> (e) IONIZING RADIATION NUMBER OF PAGES (200 words or less - underline separate)		
This project involves collaboration of LAS and several NIM institutes. It is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally x-rays and electron energy loss spectra, derived from biological specimens studied in an analytical electron microscope.		
(Page 1) (Rev. 10-81)		

Computer-based studies in ultrasonography

This project involves collaboration of LAS, with the Cardiology Branch, NHLBI. It is directed toward computer-based processing for image enhancement, pattern recognition, and three-dimensional reconstruction from ultrasound data. The principal sources of data are wide-angle, phased array echo-cardiography.

Background and Objectives: Ultrasonography allows non-invasive visualization of many organs without the hazard of ionizing radiation. Due to its safe nature and little or no patient discomfort, it is an excellent tool for screening and multiple repeat follow-up studies. Unfortunately, the presence of bone, which is completely opaque to sound waves, and certain processing practices have limited this technique. Using the computer, it is possible to overcome or circumvent many of these limitations. This project is directed toward ultrasound studies of the heart but could be expanded later to other organs.

Progress in FY80: The acquisition of real data requires the development of an esophageal transducer with interfacing to a minicomputer system. Lack of staff has resulted in deferment of this objective until FY82.

Meanwhile development of hardware (DeAnza System) and software (PICTUR) for general image processing has continued (see Nuclear Medicine and Electron Microscopy Sections).

Significance: Patients with hypertrophic cardiomyopathy have an increased risk of sudden death. Unfortunately, many of these persons are not diagnosed ante-mortem because they are asymptomatic. A reliable technique to screen those persons with a family history of hypertrophic cardiomyopathy would be of great use, because prophylactic drug therapy is probably feasible. Unfortunately, many different patterns of hypertrophy appear to exist in the population afflicted. Techniques are needed to assess the distribution of hypertrophy in those patients with uncommon distributions, especially those missed by traditional M-mode echocardiographic techniques. Additionally, it is likely that the prognosis may differ among the various patterns of hypertrophy. The use of this technique to determine regional wall motion abnormalities and other parameters of left ventricular function in patients with coronary artery disease could prove superior to the techniques of nuclear cardiology.

Proposed Course: To overcome the above mentioned problem, a phased array transducer

capable of use in the esophagus will be developed. This transducer will scan in a transverse plane. Multiple parallel images can be obtained by moving the transducer up or down in the esophagus. The transducer must be small enough to be easily tolerated by patients and will need to interface to the Varian electronics. Modifications to the existing reconstruction software will be made to permit use of the new images. Additional work is needed to capture the Varian data for image analysis and processing by the DeAnza system.

Groups of normal volunteers and patients with hypertrophic cardiomyopathy or coronary artery disease will be studied using this new method of echocardiography.

Publications and Abstracts: None

Computer Based Analysis and Image Processing in Electron Microscopy and X-ray and Electron-Loss Spectroscopy

This project involves collaboration of LAS and several NIH Institutes. It is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally X-rays and electron energy loss spectra, derived from biological specimens studied in an analytical electron microscope.

Background and Objectives: Microanalysis using electron and/or x-ray beams is a relatively new tool in biology which promises to reveal correlations between structure and function on sub-cellular and molecular levels. However, the extent to which this potential can be realized depends critically upon the use of computer methods, both in the acquisition of raw data and in the subsequent analysis of the data.

The Microscopic Analysis Section/BEIB in collaboration with CSL/DCRT is constructing a facility where digital acquisition of raw data can be performed. In the meantime several NIH investigators currently obtain raw data at other sites. The data is brought back to the NIH campus for analysis.

Of particular interest are the electron-energy loss spectra (inelastically scattered electrons) that contain information about the chemical composition of the specimen, the back-scattered electrons, and the elastically scattered electrons (both related to the mass density of various specimen regions). The physics of these various types of electrons, as well as the measured specimen current and secondary electrons emitted, needs to be elucidated in order to formulate the proper mathematical or statistical models that can combine this information into a 'true' or corrected elemental map on a pixel-by-pixel basis. These models should adjust for contributions of neighboring pixels as well as a Poisson process in some cases. The relationship between elemental (energy-loss) peaks, zero-loss (transmission) peaks, and the plasmon peaks, as well as the background contribution, requires further exploration and quantification.

The potential resolution for chemical analyses of specimens is in the range of 10-6 to 10-20 gms. and the spatial resolution is in the order of 100 to 1000 square Angstroms. In addition, maps up to 1024 x 1024 pixels can be constructed. The further development of this tool will require a new kind of image processing which will differ radically from the usual sort applied to nuclear medicine, x-ray devices,

and ultrasound.

An array processor (CSP! MAP200) has been acquired by LAS. The speed of the array processor should make several procedures fast enough to become part of normal analyses. For example, a complex FFT (1024) can be accomplished in only 20 milliseconds; a Gaussian curve fitting can be shortened from 8 hours to 10 minutes. Hence, many image processing algorithms, which can be developed offline on the DECsystem-10, can subsequently be implemented on the array processor and allowed to operate almost in realtime.

Progress During FY81: In FY80 the array processor was tested extensively and was returned to the vendor due to faults detected in a number of printed circuits and in the power supply. In FY81 the array processor was sent back to NIH, interfaced with the PDP 1160 in the BEIB Facility, and tested fully. Development of analysis programs for it is now proceeding as originally anticipated.

The DeAnza image processing system has been enlarged by the acquisition of additional hardware (a 1600 bpi tape drive and an RL02 disk drive) and by the further development of two major interactive software packages. (See project report on Nuclear Medicine.)

The PICTUR package, particularly, has been used extensively for the investigation of the characteristics of dense bodies in digitally acquired electron micrographs of platelets. Assumptions of their geometry and composition based on their two-dimensional grey scale images have been investigated. A subsection of PICTUR, ALIGN, has been used to spatially align pairs of digitized images; for example, to produce composite elemental maps from paired pre-edge and fluorine K-edge filtered images.

Significance: The ultimate biological goal is to relate structure and function at the subcellular and molecular levels. Certain active molecules (e.g., enzymes, neurotransmitters, hormones, antibodies, etc.) can be tagged with appropriate labels (e.g., fluorine) and then localized and quantified within cells by means of this tool. It should also be possible to determine the distribution of double bonds within membranes, microtubules, and cytoplasmic organelles. The distribution of elements of great biological importance (viz. calcium, magnesium, nitrogen, sulfur, and oxygen) also can be determined.

Thus, the research potential of this tool has widespread applications in all areas of biology concerned with ultrastructure, much as the development of the imaging capability of the electron

microscope itself has provided important insights in almost every area of biology.

Proposed Course: The study of the basic physics and the formulation of appropriate mathematical/statistical models needed to achieve the analytical capabilities will require extensive work with phantoms, i.e., specimens of known composition that are very thin, prepared by such means as vacuum evaporation. There will need to be extensive studies of the signal/noise ratio in phantoms and in biological specimens. Potential problems with contamination and with specimen destruction by the high energy beam also need to be studied. Sophisticated algorithms for element recognition and location, image enhancement, etc., need to be designed and, where practicable, implemented on the array processor for rapid turnaround.

LAS proposes to undertake some of these objectives in collaboration with participating wet laboratories. The DeAnza system is to be upgraded from a maximum image size of 256 x 256 to 512 x 480. Images acquired at Brookhaven are 512 x 512; hence this expansion plus the new magnetic tape drive will allow more rapid processing of the images obviating the need for data compression or partitioning.

Publications and Abstracts:

Douglas, M.A., Hui, S.W., Costa, J.L., and Bailey, J.J.: Computerized processing and subtraction of energy-filtered electron images as an aid to elemental analysis. In Bailey, G.W. (Ed.): *Proceedings of the Thirty-Eighth Meeting EMSA*. Baton Rouge, Claitor's Publishing Division, 1980, pp 128-129.

George H. Weiss, Chief

Summary of Activities

Consulting Services. George H. Weiss (PSL); James E. Kiefer (PSL); J. Shapiro (CC); A. Pikus (CC); D. F. Dillon (Walter Reed); M. Brodsky (NIDA). A statistical analysis of data comparing auditory deficits in patients with osteogenesis imperfecta, their families, and normal volunteers has been completed. Several types of auditory abnormalities have been shown to characterize both patients and close family members. These results suggest audiologic measurements as a useful diagnostic tool. Analysis of posttraumatic epilepsy in head-injured Vietnam veterans has led to a simple formula relating the time to first occurrence of postinjury fits to a cluster of symptoms. The formula, suggested in two earlier analyses, will be valuable in estimating benefits due to victims of head injury. We have developed a mathematical formalism to describe data on the rate of entrance of drug addicts to treatment facilities. The simplest one of a class of models suffices to describe the rate data for a number of years with excellent accuracy.

Theory of Biochemical Separation Techniques. George H. Weiss (PSL). This project applies mathematical methods to the interpretation of data from and the design of experiments involving ultracentrifugation, electrophoresis, and chromatography. Little, outside of planning for an experiment to determine optimal methods for determining molecular weight distributions, was done this year. On the completion of equipment by Marc Lewis (BEIB) the experiments will be started.

Actin in Nonmuscle Cells--Biophysical and Biochemical Studies. Stephen L. Brenner (PSL). Studies on the mechanism of polymerization of actin have led to the discovery of monomer actin ATPase activity. Further kinetic studies are being pursued to verify a new species of monomeric actin.

Theory and Application of Nuclear Magnetic Resonance Spectroscopy. James A. Ferretti (PSL); G. H. Weiss (PSL); J. E. Kiefer (PSL); R. J. Highet (NHLBI). Experiments utilizing two dimensional Fourier transform spectroscopy have been

performed on a number of molecules. The technique allows an order of magnitude of greater accuracy than the comparable one-dimensional methods. An investigation of the accuracy of measuring chemical shifts has been completed and a number of improvements to present practice have been suggested.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph J. Nossal (PSL). Techniques are being developed for the application of laser Doppler techniques to measure blood flow in tissue microvasculature. The theory that has been worked out has been found in excellent agreement with experiments on artificial blood cells. A theory is presently under development for interpreting experiments on blood flow in muscle.

Cell Motility and Chemotaxis. Ralph J. Nossal (PSL). Little has been done on this project in the past year.

Theory and Measurement of Intermolecular Forces. V. Adrian Parsegian (PSL); M. Prouty (PSL); B. K. Lee (PSL); A. N. Schechter (NIADDK); R. P. Rand (Brock University). Measurements of intermolecular forces in proteins or nucleic acids using the osmotic stress methods developed in this Laboratory are now underway. Because sickle cell hemoglobin has been gelled, the investigators will undertake a systematic measurement of thermodynamic data on gelation and crystallization. B. K. Lee has written a number of programs to integrate crystallographic data on proteins into a project that will explore the way that proteins assemble into more complicated structures.

Studies in Mathematics and Statistics. George H. Weiss (PSL); J. E. Kiefer (PSL). A review article on random walks in chemical physics was completed. A study of order statistics of diffusion processes is presently underway.

Diffusion of Molecules on Cell Surfaces and Light Scattering from Fluids. Nahum Gershon (PSL); B. Aizenbud (MIT). The investigators have found that

INSTITUTION (PLEASE PRINT FULL NAME AND ADDRESS)	NAME, GRADE AND OFFICE AFFILIATION, AND TITLE OF PRINCIPAL INVESTIGATOR, AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED IN THE PROJECT	PROJECT NUMBER
PHYSICAL SCIENCES LABORATORY UNIVERSITY OF CALIFORNIA, SAN DIEGO LA JOLLA, CALIF. 92037	GEORGE H. WEISS, Chief, PSL, DORT James E. Aheer, PSL, DORT	701 CT 00002-14 PSL
PERIOD COVERED October 1, 1980 to September 30, 1981 (Title of project (if appropriate or leave blank))		
Consulting Services		
NAME, GRADE AND OFFICE AFFILIATION, AND TITLE OF PRINCIPAL INVESTIGATOR, AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED IN THE PROJECT		
PI: George H. Weiss, Chief, PSL, DORT James E. Aheer, PSL, DORT		
COLLABORATING UNITS (If any): R. A. Brooks, Ph.D., SN, MRCDS; J. Shapiro, M.D., CC, DMR; A. Pinsky, M.Sc., CC, DMR; W. F. Caveness, M.D. (deceased); David Dillon, M.D., Walter Reed; M. Brodsky, M.D.; S. Knecht, L.M., DORT; D. Feeney, Ph.D., D. of N.M.; E. Laska, Ph.D., Rockland State Hospital.		
THEORY OF BIOCHEMICAL SEPARATION TECHNIQUES		
This project explores the use of mathematical techniques applied to the interpretation of experiments in biochemistry. Preparations to collect data on fractionated serum albumin are being made by Dr. Marc Lewis. Until data collection equipment is installed on Dr. Lewis' ultracentrifuge no progress is possible on the contemplated study.		

the effect of surface curvature does not greatly affect diffusion constants calculated using fluorescence photobleaching recovery methods. The light scattering spectrum from viscoelastic fluids was derived.

Quantitative Analysis of the Electronmicroscopy of Cells and their Plasma Membrane. Nahum Gershon (PSL); P. Gorden (NIADDK); K. Porter (U. Colorado); L. Jarett (U. of Pennsylvania). Work is in progress on the analysis of hormone binding to their receptors on cell membranes using statistical analysis of digitized electronmicrographs. In particular, a study was completed on the spatial distribution of binding sites by cytochalasins B and D.

Computerized Typesetting of Scientific Papers.

V. Adrian Parsegian (PSL); N. Crawford (PSL); M. Douglas (LAS); M. Horton (LAS); M. McNeel (PSL); P. Miller (OD); J. Prewitt (OD); R. Fajman (CCB); J. Fajman (CCB). This project is intended to produce magnetic tape versions of material for publication, for direct typesetting. A program is presently being written to write tapes on the IBM System 370 using WYLBUR. The tape writing program is also being generalized to prepare manuscripts for several journals.

INSTITUTION (PLEASE PRINT FULL NAME AND ADDRESS)	NAME, GRADE AND OFFICE AFFILIATION, AND TITLE OF PRINCIPAL INVESTIGATOR, AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED IN THE PROJECT	PROJECT NUMBER
PHYSICAL SCIENCES LABORATORY UNIVERSITY OF CALIFORNIA, SAN DIEGO LA JOLLA, CALIF. 92037	GEORGE H. WEISS, Chief, PSL, DORT James E. Aheer, PSL, DORT	701 CT 00014-14 PSL
PERIOD COVERED October 1, 1980 to September 30, 1981 (Title of project (if appropriate or leave blank))		
Theory of Biochemical Separation Techniques		
This project explores the use of mathematical techniques applied to the interpretation of experiments in biochemistry. Preparations to collect data on fractionated serum albumin are being made by Dr. Marc Lewis. Until data collection equipment is installed on Dr. Lewis' ultracentrifuge no progress is possible on the contemplated study.		

Research Projects

Consulting Services

Members of the PSL provide consulting services in several areas of applied mathematics and the physical sciences to researchers at NIH and elsewhere. We have completed a study on the phantom view method in computerized tomography, finding that it is effective at diminishing certain undesirable streak artifacts. A considerable amount of work was spent on the study of audiologic defects in patients with osteogenesis imperfecta. An analysis of post traumatic epilepsy in head-injured Vietnam veterans is being completed and a model that fits data very well on the rate of occurrence of fits has been developed. A mathematical model for the entrance of drug addicts into treatment facilities was devised and shown to give an excellent fit to available data. Several combinatorial problems related to computer storage were solved to yield asymptotic formulae.

A study of the phantom view method for diminishing image artifacts due to interpolation in computerized tomography has been completed with Dr. Rodney Brooks and a paper has been submitted for publication.

Study of the occurrence of posttraumatic epilepsy in a group of head-injured veterans has shown that the occurrence of epileptic fits in different injury categories follows a negative exponential distribution to a good approximation. The incidence varies with severity of injury but the average time to first fit appears to be independent of injury. Further work has gone into planning a second phase of the study of these veterans, in which as many as possible will be called in for an extensive examination. Several questions can then be answered that are presently obscured by a non-uniform follow up time.

A study of audiologic defects in patients with osteogenesis imperfecta has shown that there is a marked excess of audiologic defects both in diseased patients and in otherwise unaffected close relatives. Further investigations are planned. Dr. Susan Hauser, CSL, DCRT, has coupled a digitizer to the Clinical Center otoadmittance meter allowing the collection of data with a previously unattainable accuracy. A study of the features of normal tympanograms will be undertaken with the new equipment.

Together with M. Brodsky we have developed a model for the rate of entrance of drug addicts into treatment facilities. The model gives a good fit to the data and allows early prediction of the number of

addicts in a given cohort to use these facilities.

Several combinatorial problems were solved for Dr. Gary Knott, LSM, DCRT, which will be used in the analysis of computer data storage algorithms.

Keyword Descriptors: Image reconstruction, interpolation, computerized tomography, audiologic defects, osteogenesis imperfecta, mathematical models.

Publications:

- Meirowsky, A. M., Caveness, W. F., Rish, B. L., Dillon, J. D., Mohr, J. P., Kistler, J. P., and Weiss, G. H.: Cerebrospinal fluid complicating missile wounds of the brain. *J. Neurosurgery* 54 44-47, 1981
- Mohr, J. P., Weiss, G. H., Caveness, W. F., Dillon, J. D., Meirowsky, A. M., and Rish, B. L.: Language and motor deficits following penetrating head injuries in Vietnam. *Neurology* 30 1273-1279, 1980.
- Rish, B. L., Dillon, J. D., Caveness, W. F., Mohr, J. P., Kistler, J. P., and Weiss, G. H.: The evolution of craniotomy as a debridement technique for penetrating craniocerebral injuries. *J. Neurosurgery* 53 772-775, 1980.

Theory of Biochemical Separation Techniques

This project explores the use of mathematical techniques applied to the interpretation of experiments in biochemistry. Preparations to collect data on fractionated serum albumin are being made by Dr. Marc Lewis. Until data collection equipment is installed on Dr. Lewis' ultracentrifuge no progress is possible on the contemplated study.

Keyword Descriptors: Biochemical separation, ultracentrifugation, enzyme kinetics.

Publications:

- Weiss, G. H.: Can one measure rate constants using chromatographic methods? *Separation Sci.* 16 75-80, 1981
- Weiss, G. H., and Darvey, I. G.: A note on the choice of substrate concentration in enzyme kinetics. *J. Theoretical Biology* (in press)

DATE: JAN 1980 (ACT) (10/1/80) (10/1/80) (10/1/80) PROJECT NUMBER: (10/1/80) (10/1/80) (10/1/80)		TO: DEPARTMENT OF HEALTH AND HUMAN SERVICES FROM: NATIONAL RESEARCH SERVICE PROJECT NUMBER: Z01 CT 00040-03 PSL	
PERIOD COVERED: October 1, 1980 to September 1, 1981 TITLE OF PROJECT (40 characters or less): Actin in Nonmuscle Cells - Biophysical and Biochemical Studies			
SUMMARY, LABORATORY AND RESEARCH AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED IN THE PROJECT: PI: Stephen L. Brenner, Research Chemist, PSL, OCR Other: E. D. Korn, Chief, LBS, NMLBI			
COOPERATING UNITS (4 x 4): Laboratory of Cell Biology, NMLBI			
LAB/BRANCH: Physical Sciences Laboratory SECTION:			
INSTITUTION AND LOCATION: Division of Computer Research and Technology TOTAL PERSONNEL: 1.0 PROFESSIONAL: 1.0 OTHER: 0.0 OTHER APPROPRIATE BUDGETS: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) MATERIALS <input type="checkbox"/> (d) MINORS <input type="checkbox"/> (e) INTERVIEWS SUMMARY OF WORK (100 words or less - underline key words): Studies were continued on the mechanism of polymerization of the protein actin, a major component of the motile apparatus of all eukaryotic cells. A monomer actin ATPase activity was discovered. Kinetic analysis of the effects of the drug cytochalasin, which accelerates this ATPase activity, have led to the postulation of a new species of monomeric actin that may be an essential intermediate in actin polymerization.			

PH-6040
(Rev. 2-6-82)

DATE: JAN 1980 (ACT) (10/1/80) (10/1/80) (10/1/80) PROJECT NUMBER: (10/1/80) (10/1/80) (10/1/80)		TO: DEPARTMENT OF HEALTH AND HUMAN SERVICES FROM: NATIONAL RESEARCH SERVICE PROJECT NUMBER: Z01 CT 00025-06 PSL	
PERIOD COVERED: October 1, 1980 to September 1, 1981 TITLE OF PROJECT (40 characters or less): Theory and Application of Nuclear Magnetic Resonance Spectroscopy			
SUMMARY, LABORATORY AND RESEARCH AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED IN THE PROJECT: PI: James A. Ferretti, Ph.D., Research Chemist, PSL, OCR G. R. Marshall, Ph.D., Professor of Physiology, Department of Physiology and Biophysics, Washington University School of Medicine, St. Louis, MO Rollie J. Myers, Ph.D., Professor of Chemistry, Department of Chemistry, University of California, Berkeley, CA James A. Kiefer, and G. W. Weiss, Ph.D., Chief, PSL, OCR R. J. Hight, Ph.D., Laboratory of Chemistry, NMLBI Lance R. Fohl, Ph.D., Terence A. Marks, Ph.D., and Jack S. Henson, Ph.D., Laboratory of Clinical Pharmacology, NMLBI William M. Egan, Ph.D., Bureau of Biologics, FDA, Bethesda, MD Norman Dineley, Ph.D., Professor of Chemistry, Louisiana State University, Baton Rouge, LA			
COOPERATING UNITS (4 x 4): Lab/BRANCH: Physical Sciences Laboratory SECTION:			
INSTITUTION AND LOCATION: Division of Computer Research and Technology TOTAL PERSONNEL: 1.1 TOTAL (LOCAL): 1.0 OTHER: 0.1 OTHER APPROPRIATE BUDGETS: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) MATERIALS <input type="checkbox"/> (d) MINORS <input type="checkbox"/> (e) INTERVIEWS SUMMARY OF WORK (100 words or less - underline key words): The purpose of this project is to develop new methods in nuclear magnetic resonance spectroscopy, to extend and determine the utility of existing techniques, and to apply these techniques to structural problems in organic molecules and conformational problems in small peptides and proteins. Of current interest is the development of two-dimensional Fourier transform NMR spectroscopy. The importance of this technique is that it permits one to restrict one nuclear parameter to one dimension and a second parameter to the other dimension. A second part of the project is to determine best data processing techniques for precise determination of chemical shifts.			

PH-6040
(Rev. 2-6-82)

Actin in Nonmuscle Cells--Biophysical and Biochemical Studies

Studies were continued on the mechanism of polymerization of the protein actin, a major component of the motile apparatus of all eukaryotic cells.

A monomer actin ATPase activity was discovered. Kinetic analysis of the effects of the drug cytochalasin, which accelerates this ATPase activity, have led to the postulation of a new species of monomeric actin that may be an essential intermediate in actin polymerization.

Actin is one of the major proteins of the cytoskeleton of all eukaryotic cells. As such, it is involved in many different motile processes and in the regulation of cell shape and cell organization. Actin is a globular molecule of molecular weight 42,000 that polymerizes into double helical filaments under ionic conditions similar to those of the cytoplasm of cells.

It is in this polymerized form (microfilaments) that actin presumably functions in non-muscle cells just as it is the polymerized form of actin (the thin filaments) that functions in muscle contraction. In contrast to the situation in muscle, most of the actin in non-muscle cells is unpolymerized and its polymerization is spatially and temporally regulated so that the microfilaments occur in the cell when and where they are needed for specific motile events. The regulation of actin polymerization has been the focus of our research this year.

1. Identification of a new species of monomeric actin. We have shown in the past two years that the cytochalasins, a group of natural products that are potent inhibitors of a variety of motile processes in eukaryotic cells, have pronounced effects on actin polymerization in vitro. One of these effects is the uncoupling of actin ATPase activity from actin polymerization. Normally, when polymerization occurs, a monomer actin bound ATP is hydrolyzed to polymer bound ADP. Cytochalasins greatly increase the rate of ATP hydrolysis even while inhibiting actin polymerization. We have now shown that this effect is due to the acceleration of a monomeric actin ATPase cycle, which can exist independent of the ATPase associated with monomer addition to polymer. Kinetic analysis of the effects of four cytochalasins on actin from two sources (rabbit muscle and Acanthamoeba, a soil amoeba) requires the existence of an until now unknown species of actin monomer. Formation of this intermediate is the rate determining step in the monomer ATPase cycle when cytochalasins are present. In the absence of cytochalasins, disappearance of this intermediate is

rate limiting. The coupling of the monomer ATPase cycle to the polymerization of actin, and the possible role of the newly discovered actin species as an obligatory intermediate in actin polymerization, are under investigation.

2. Equilibrium Studies of Actin Polymerization. It is now clear that the polymerization of actin ATP is extremely complex (see above). Actin with bound ADP will also polymerize. The result is an equilibrium system of actin filaments (containing bound ADP) and monomeric ADP actin. The ADP actin system may provide a useful tool for understanding actin polymerization since it uncouples the polymerization process from the hydrolysis of nucleotide in an equilibrium, rather than a steady-state system. We have begun a detailed study of ADP actin polymerization using the techniques of ultracentrifugation, high-shear viscometry, and light scattering.

Because ATP hydrolysis is not obligatory for actin to polymerize, and because cellular energy stores are depleted when ATP is used, we continue to search for a role for nucleotide hydrolysis in actin polymerization. It is possible that it is at the level of the monomeric actin, and not the hydrolysis associated with polymerization per se, at which regulation is affected. Efforts will be made to examine this idea through the use of nonhydrolyzable ATP analogs, cytochalasins, and inhibitors or promoters of actin ATPase activity as well as purified proteins known to have direct effects on the state of actin assembly.

Keyword Descriptors: polymerization, actin, cytochalasin, cytoskeleton, eukaryotic.

Publications:

Brenner, S. L., and Korn, E. D.: Stimulation of actin ATPase activity by cytochalasins provides evidence for a new species of monomeric actin. *J. Biol. Chem.* (in press).

Theory and Application of Nuclear Magnetic Resonance Spectroscopy

The purpose of this project is to develop new methods in nuclear magnetic resonance spectroscopy, to extend and determine the utility of existing techniques, and to apply these techniques to structural problems in organic molecules and conformational problems in small peptides and proteins. Of current interest is the development of two-dimensional Fourier transform NMR spectroscopy. The importance of this technique is that it permits one to restrict one nuclear parameter to one dimension and a second parameter to the other dimension. A second part of the project is to determine best data processing techniques for precise determination of chemical shifts.

Since the acquisition of the NT-360 NMR spectrometer 18 months ago, we have been carrying out various experiments on complex organic and biological molecules, which were heretofore impossible. The major emphasis in this project has been the application of multiple pulse and two-dimensional Fourier transform NMR spectroscopy. The principal idea behind multiple pulse experiments is to map out the behavior of the nuclear magnetization during an evolution period as well as during a detection period after the last radio frequency pulse. Because this permits many choices for the second frequency axis, the advantages of two-dimensional spectroscopy are numerous and include: correlating frequencies of pairs of nuclei to simplify assignments, improving spectral resolution, measuring cross relaxation processes for distance determinations, and studying multiple quantum coherence phenomena.

In one study, we have determined the structures of two stereoisomeric metabolites isolated by HPLC from the bile of rats treated intraperitoneally with bromobenzene. The 2D J spectra of both metabolites permitted complete resolution of all the transitions and allowed us to carry out the assignments of lines. These results demonstrated that the metabolites were formed by the opening of aryl epoxide intermediates by glutathione. This study also enabled us to demonstrate the feasibility of studying spectra in the presence of a strong water peak.

We are applying a three-pulse experiment followed by a two-dimensional Fourier transformation to investigate cross relaxation pathways in rigid organic molecules. Cross relaxation analysis allows the estimation of internuclear distances, yields rotation correlation times, and produces information on molecular complexes. We have carried out such

INTERAGENCY COORDINATION (MANDATORY) PROJECT NUMBER (DO NOT USE THIS SPACE)	DEPT. OF HEALTH AND HUMAN SERVICES NATIONAL INSTITUTE OF HEALTH INTRAMOLECULAR RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00023-10 PSL
PERIOD COVERED October 1, 1980 to September 30, 1981 TITLE OF PROJECT (40 characters or less) Correlation Function Spectroscopy/Laser Light Scattering		
NAME, ADDRESS AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT PI: R. J. Nossal, Ph.D., Research Physicist, PSL, DERT		
COOPERATING UNITS (if any) J. Glader, Ph.D., LBC, NIADDA R. Bonner, Ph.D., BEIB, ORS P. D. Dondos, LDC, NIDDK		
INSTITUTION AND LOCATION Division of Computer Research and Technology (FILL IN) PHYSICAL SCIENCES LABORATORY PHYSICAL SCIENCES LABORATORY (CHECK AN APPROPRIATE BOX) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a) MINDS <input type="checkbox"/> (b) INTERFERENCE SUMMARY OF WORK (200 words or less - underline responses)		
Experimental and theoretical studies have been performed to develop laser induced light scattering methods for studying biological cells, viscoelastic polymer solutions, and similar materials. Studies also are being performed in order to understand how laser Doppler techniques can be used to measure blood flow in tissue microvasculature.		

7-750 (Rev. 2-82)

INTERAGENCY COORDINATION (MANDATORY) PROJECT NUMBER (DO NOT USE THIS SPACE)	DEPT. OF HEALTH AND HUMAN SERVICES NATIONAL INSTITUTE OF HEALTH INTRAMOLECULAR RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00027-09 PSL
PERIOD COVERED October 1, 1980 to September 30, 1981 TITLE OF PROJECT (40 characters or less) Cell Motility and Chemotaxis		
NAME, ADDRESS AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT PI: R. J. Nossal, Research Physicist, PSL, DERT		
COOPERATING UNITS (if any) PHYSICAL SCIENCES LABORATORY PHYSICAL SCIENCES LABORATORY (CHECK AN APPROPRIATE BOX) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (a) MINDS <input type="checkbox"/> (b) INTERFERENCE SUMMARY OF WORK (200 words or less - underline responses)		
This project has been undertaken to study various aspects of cell locomotion, including the mathematical basis of microscopic assays for leukocyte chemotaxis. New procedures for measuring parameters of cell migration, including computer assisted tracking techniques, are being developed. Mathematical relationships between microscopic cell motion and macroscopic response are derived.		

7-750 (Rev. 2-82)

studies on veratraldehyde and a series of Enkephalin analogs. Specific interactions are demonstrated in the Enkephalin derivatives. We are attempting to quantitate the results on veratraldehyde in order to evaluate the competitive inter- and intramolecular dipolar contributions to the nuclear Overhauser enhancement factor.

We are continuing to study molecular motions in oligopeptides using spin-lattice relaxation times, spin-spin relaxation times, and NOE factors as well as using the two-dimensional techniques for structural investigations on these systems. We are attempting a complete assignment of the proton spectrum of Bleomycin. We have carried out a complete temperature and field dependence study on Bradykynin and evaluated the motional parameters. We have also carried out a study on liver alcohol dehydrogenase, by investigating the cadmium-113 chemical shifts where the cadmium-113 replaced Zinc at both the catalytic and non-catalytic sites. We are attempting to learn more about the nature of the metal ion coordination at the catalytic site.

We have investigated, by a simulation study, the error in measured chemical shifts when various strategies are used for filtering and smoothing the data and for estimating peak position. We have found that curve-fitting the data in a neighborhood of the observed maximum is always considerably more accurate than simply choosing the position of the peak maximum as the true maximum. Further, the use of a matched filter leads to a considerable improvement over the use of no filter, and the improvement is not sensitive to the choice of filter constant.

Keyword Descriptors: Nuclear Magnetic Resonance, two-dimensional, Fourier transform, bile metabolite, liver alcohol dehydrogenase, Enkephalin.

Publications:

- Egan, W., Ferretti, J. A., and Marshall, G. R.: Relaxation parameters and motional properties in biological macromolecules. *Bull. Magnet. Resonance* 2:15-17, 1981.
- Ferretti, James A., Highet, Robert J., Pohl, Lance R., Marks, Terrence R., and Hinson, Jack A.: Application of 2D J-resolved spectroscopy in the structural investigation of bile metabolites. Abstract, 22nd Experimental NMR Conference, 1981.
- Gupta, R. K., Ferretti, J. A., Becker, E. D., and Weiss, G. H.: A modified fast inversion recovery technique for spin-lattice relaxation measurements. *J. Magnet. Resonance* 38:447-452, 1981.
- Weiss, G. H., Ferretti, J. A., and Kiefer, J. E.: A study of precision in the measurement of chemical shifts. *J. Magnet. Resonance* (in press).

Correlation Function Spectroscopy/Laser Light Scattering

Experimental and theoretical studies have been performed to develop laser inelastic light scattering methods for studying biological gels, viscoelastic polymer solutions, and similar materials. Studies also are being performed in order to understand how laser Doppler techniques can be used to measure blood flow in tissue microvasculature.

Quasielastic light scattering has been used to study dynamical properties of various biological substances and model systems. Emphasis has been on developing novel applications of this relatively new technology and on devising physical and mathematical theories in support of experimental protocols. Current work continues on schemes for 1) non-invasive surveillance of blood flow and 2) non-perturbative probes of the mechanical properties of soft polymer gels similar to those found in biological cells and within tissue interstitia.

A collaboration with R. Bonner (BEIB, DRS) and P. Bowen (NHLBI) has resulted in publication of a theory which relates quasielastic light scattering measurements to blood flow in tissue microvasculature. This theory accounts for diffuse scattering by immobile tissue constituents and for multiple interactions of photons with moving blood cells. The theory has been tested with an experimental analog in which particles flow through a fiber capillary bundle imbedded in a composite gel, the latter containing polymer microspheres which impart optical properties characteristic of those of biological tissue. Dr. Bonner and Mr. Bowen have been using their laser Doppler flowmeter in various clinical studies and we have continued to collaborate on related theoretical and experimental problems. Attempts currently are being made to provide a theory for interpreting measurements of tissue blood flow in moving heart muscle.

Efforts to apply quasielastic light scattering to studies of dilute polymer networks recently have involved improvements in instrumentation and development of methodology for measuring lattice damping parameters ('internal viscosity'). An apparatus has been constructed to facilitate torsional excitation of a sample by an external mechanical field. Also, a fiber optics version of the spectrometer has been developed which promises to be particularly useful for studying small specimens. Data have been acquired to characterize the dependence of internal dissipation on such variables as polymer concentration, crosslink density, and solvent viscosity; also, we have begun work on a theory to relate those measurements to microscopic physical

properties of a gel. Our collaboration with Dr. J. Gladner (NIADDK), on studies of the biophysical chemistry of polymer networks which arise during blood coagulation, has been reinitiated.

Keyword Descriptors: Laser light scattering macromolecules, diffusion coefficients, correlation functions, gels, blood flow, Doppler flowmeter.

Publications:

Bonner, R., and Nossal, R. A model for laser Doppler measurements of blood flow in tissues. *Applied Optics* 20:2097-2108, 1981.

Nossal, R.: Quasielastic light scattering from polymer gels. In Chen, S. H., Chu, B., and Nossal, R. (Eds.): *Scattering Techniques Applied to Supramolecular and Nonequilibrium Systems*. New York, Plenum Publ. Corp. (in press).

Nossal, R., and Jolly, M. Shear waves in cylindrical gels. *J. Appl. Phys.* (in press)

Cell Motility and Chemotaxis

This project has been undertaken to study various aspects of cell locomotion, including the mathematical basis of macroscopic assays for leukocyte chemotaxis. New procedures for measuring parameters of cell migration, including computer assisted tracking techniques, are being developed. Mathematical relationships between microscopic cell motion and macroscopic response are derived.

This study relates to cell locomotion and chemotaxis. Recent emphasis has been on examining certain immunologic aspects of leukocyte migration and on constructing physical models of signal transduction occurring at the surfaces of chemoresponsive cells.

During the past year this project has been carried on with reduced effort while laboratory personnel have been otherwise occupied (cf. project Z01-CT00021-10 PSL). Literature searches have been performed in order to identify in vitro models of polymerizing cytoskeletal structures which might be amenable to study by recently developed quasielastic laser light scattering techniques. Attention also has been given to assimilating information on physical theories concerning detection of chemotoxins by receptors at the surfaces of motile cells. A previously prepared review of mathematical theories of chemotactic responses was published.

Keyword Descriptors: Cell locomotion, leukocyte chemotaxis, capillary migration assays.

Publications:

Nossal, R.: Mathematical theories of topotaxis. In Jager, W., Rost, H., and Tautu, P. (Eds.): *Biological Growth and Spread. Mathematical Theories and Applications*. Heidelberg, Springer-Verlag, 1980, pp. 410-440.

INTERMOLECULAR FORCES (DO NOT WRITE IN THESE SPACES) PROJECT NUMBER: 201 CT 00026-De PSL	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF INTERACTIONS RESEARCH PROJECT	PROJECT NUMBER: 201 CT 00026-De PSL
PERIOD COVERED: October 1, 1980 to September 30, 1981 TITLE OF PROJECT (DO NOT WRITE IN THESE SPACES)		
Theory and Measurement of Intermolecular Forces NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONNEL PARTICIPATING IN THE PROJECT		
PI: V. A. Parsanian, Ph.D., PSL, DCRT Others: B. A. Lee, Ph.D., PSL, DCRT R. P. Wand, Ph.D., Brock University N. Leong-Millman, Ph.D., Queen's University N. Fuller, Brock University D. Rau, Ph.D. M. Priety, Ph.D., LCB, NIAID A. N. Schechter, M.D., LCB, NIAID G. H. Weiss, Ph.D., PSL, DCRT		
COOPERATING UNITS (if any)		
LABORATORY: Physical Sciences Laboratory		
INSTITUTION AND LOCATION: Division of Computer Research and Technology		
TOTAL MANPOWER: 3.5 PROFESSIONAL: 3.0 OTHER: 0.5		
SCOPE OF RESEARCH (DO NOT WRITE IN THESE SPACES)		
(a) MAIN SUBJECTS (b) HUMAN ISSUES (c) OTHER		
(a) MAIN SUBJECTS (b) HUMAN ISSUES (c) OTHER		
SUMMARY OF WORK (DO NOT WRITE IN THESE SPACES)		
Our capacity to determine intermolecular forces in aqueous or physiological milieu now covers proteins and nucleic acids, as well as phospholipid bilayer membranes. There is good evidence that hydration forces dominate interactions near contact. These forces are due to the disturbance of water by charges. Exponentially decaying hydration forces, first characterized quantitatively on the exterior of large molecules or aggregates. They depend on the chemical identity and packing of water polar soluble groups on the membrane surface. They vanish when an opposing body sticks more strongly to these water soluble groups than does water. Measurements of intermolecular forces in proteins or nucleic acid are now underway using osmotic stress methods developed for membranes. Evidence is strong for the action of hydration forces between parallel DNA double helices. Programs written on the DCRT Molecular Display system are being developed to examine contacts between proteins in crystals and between nucleic acids in condensed arrays.		
(New 201)		

INTERMOLECULAR FORCES (DO NOT WRITE IN THESE SPACES) PROJECT NUMBER: 201 CT 00026-De PSL	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF INTERACTIONS RESEARCH PROJECT	PROJECT NUMBER: 201 CT 00026-De PSL
PERIOD COVERED: October 1, 1980 to September 30, 1981 TITLE OF PROJECT (DO NOT WRITE IN THESE SPACES)		
Studies in Mathematics and Statistics		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONNEL PARTICIPATING IN THE PROJECT		
PI: George H. Weiss, Chief, PSL, DCRT Other: James E. Kiefer, PSL, DCRT		
COOPERATING UNITS (if any)		
LABORATORY: Physical Sciences Laboratory		
INSTITUTION AND LOCATION: Division of Computer Research and Technology		
TOTAL MANPOWER: 0.5 PROFESSIONAL: 0.5 OTHER: 0.3		
SCOPE OF RESEARCH (DO NOT WRITE IN THESE SPACES)		
(a) MAIN SUBJECTS (b) HUMAN ISSUES (c) OTHER		
(a) MAIN SUBJECTS (b) HUMAN ISSUES (c) OTHER		
SUMMARY OF WORK (DO NOT WRITE IN THESE SPACES)		
A comprehensive review article on the applications of random walk methods in chemical physics is in the process of completion. A study of some order statistics related to random walks and diffusion processes has been com- pleted. Several statistical problems related to the matching of DNA sequences are under investigation.		
(New 201)		

Theory and Measurement of Intermolecular Forces

Our capacity to determine intermolecular forces in aqueous or physiological milieu now covers proteins and nucleic acids as well as phospholipid bilayer membranes. There is good evidence that hydration forces dominate interactions near contact. These forces are due to the disturbance of water by charges on the exterior of large molecules or aggregates.

Exponentially decaying hydration forces, first characterized quantitatively between bilayer membranes, are typically repulsive. They depend on the chemical identity and packing of water polar soluble groups on the membrane surface. They vanish when an opposing body sticks more strongly to these water soluble groups than does water.

Measurements of intermolecular forces in proteins or nucleic acid are now underway using osmotic stress methods developed for membranes. Evidence is strong for the action of hydration forces between parallel DNA double helices.

Programs written on the DCRT molecular display system are being developed to examine contacts between proteins in crystals and between nucleic acids in condensed arrays.

Our activities this year have been to examine the consequences on membrane processes of earlier measurements of forces between bilayer membranes and to develop several methods for identifying and measuring forces experienced by proteins and nucleic acids.

Beginning from the systematic determination of electrostatic, dispersion, and hydration forces between a large range of phospholipid bilayer membranes, we have been able to correlate the intermembrane forces with the ability or inability of vesicular membranes to fuse. Exponentially growing hydration repulsive forces dominate below 30 angstroms separation. Their strength varies with the density and identity of water soluble groups on the membrane surface. This repulsive force collapses upon addition of substances, such as calcium, with phosphatidylserine membranes that bind more strongly than does water to these water soluble groups.

Electrostatic interactions, seen beyond 20 to 30 angstroms membrane separation, almost follow the behavior expected from double layer theory. A systematic deviation from that theory gives evidence for perturbation of water structure around ions in solution.

Methods of measurement analogous to those used to determine membrane-membrane forces are now successfully being applied to the aggregation, gelation and crystallization of proteins and to the packing of parallel double helical strands of DNA. Sickel cell hemoglobin has been successfully gelled (Prouty, Schechter) under conditions where one can measure the work of removal of water from the protein and water mixture. Systematic collection of thermodynamic data on gelation and crystallization now appears feasible. Similarly measurements on the repulsive force versus separation curve for parallel DNA helices are now in progress.

These molecular studies are complemented by a major study of protein and nucleic acid contact using the DCRT molecular graphics facility. To this end a computer program has now been written (Lee) to construct protein crystal structures by combining atomic coordinates with the crystal symmetry. As in previous studies of contacts stabilizing protein dimers and tetramers, the stable association of peptides involves close approach and tight fits. We expect that the lessons learned from these studies will be helpful in work anticipated on the self assembly of elaborate protein structures.

Keyword Descriptors: phospholipid bilayer membranes, hydration forces, electrostatic forces, dispersion forces, ionic solutions, protein gelation, nucleic acids.

Publications:

- Lis, L. J., Lis, W. T., Parsegian, V. A., and Rand, R. P.: Adsorption of divalent cations to a variety of phosphatidylcholine bilayers. *Biochemistry* 20:1771-1777, 1981.
- Lis, L. J., McAlister, M., Fuller, N., Rand, R. P., and Parsegian, V. A.: Interactions between neutral phospholipid bilayer membranes. *Biophys. J.* (in press).
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- Lis, L. J., Parsegian, V. A., and Rand, R. P.: Binding of divalent cations to dipalmitoylphosphatidylcholine bilayers and its effect on bilayer interaction. *Biochemistry* 20:1761-1770, 1981.
- Parsegian, V. A.: Forces between membranes approaching contact. *Scandinavian J. of Clinical Investigation* 41:156, 39-47, 1981.
- Parsegian, V. A., Rand, R. P., and Stamatoff, J.: Perturbation of membrane structure by uranyl acetate labeling. *Biophys. J.* 33:475-478, 1981.
- Parsegian, V. A., and Weiss, G. H.: Spectroscopic parameters for computation of van der Waals forces. *J. Colloid Interface Sci.* 81:285-289, 1981.

Studies in Mathematics and Statistics

A comprehensive review article on the applications of random walk methodologies in chemical physics is in the process of completion. A study of some order statistics related to random walks and diffusion processes has been completed. Several statistical problems related to the matching of DNA sequences are under investigation.

A review article on random walks in chemical physics is being completed and will be submitted to *Advances in Chemical Physics*. In addition we have applied some rigorous results on the number of distinct sites visited in a finite random walk to the study of materials with trapping sites. Together with R. J. Rubin we have developed statistical results on the probability of visiting a set of points by a lattice random walk and with M. F. Shlesinger we have studied properties of the expected number of distinct sites visited during an n-step lattice random walk. We have studied order statistics of diffusing particles. Together with K. E. Shuler we are analyzing combinatorial problems related to the matching of DNA sequences. These problems are currently studied by simulation techniques, leading to results of questionable generality, but some analytic progress is possible and some results on matching probabilities have been obtained.

Keyword Descriptors: Random walks, diffusion processes, trapping sites, first passage time problems, sequence matching.

Publications:

- Kiefer, J. E., and Weiss, G. H.: A comparison of two methods for accelerating the convergence of Fourier series. *Computers and Mathematics* (in press).
- Lindenberg, K., Seshadri, V. E., Shuler, K. E., and Weiss, G. H.: Lattice random walks for sets of random walkers. *J. Statistical Physics* 23 11-25, 1980.
- Oppenheim, I., Shuler, K. E., and Weiss, G. H.: Stochastic processes. In Lerner, R. G., and Trigg, G. L. (Eds.): *Encyclopedia of Physics*. New York, Addison-Wesley, 1980, pp. 964-967.
- Weiss, G. H.: Asymptotic form for random walk survival probabilities on 3-D lattices with traps. *Proc. Natl. Acad. Sci. USA* 77:1273-1274, 1980.
- Weiss, G. H.: First passage times for one dimensional random walks. *J. Statistical Physics* 24:581-589, 1981.
- Weiss, G. H.: Note on lattice random walks with an excluded point. *J. Mathematical Physics* 22:562-563, 1981.
- Weiss, G. H., and Shlesinger, M. F.: On the expected number of distinct points in a subset visited by an N-step random walk. *J. Statistical Physics* (in press).

Quantitative Analysis of the Electronmicroscopy of cells and their plasma membranes

In this study, the distributions of insulin binding sites on the surface of rat adipocytes and liver plasma membranes were studied using monomeric ferritin-insulin viewed by electronmicroscopy and analyzed by newly developed quantitative methods. It shows that insulin binding sites are non-randomly distributed on rat adipocyte cell surfaces while they are uniformly distributed on liver plasma membranes. The quantitative characteristics of the receptor groups and the mode of action of cytochalasin B and D have been elucidated.

In the second part we have been looking at the organization of intramembraneous particles on lymphocytes and coated pits on adipocyte-like fibroblasts.

In the third part of this investigation, the three dimensional structure of polymerization centers for macromolecules in cells has been pursued using three-dimensional reconstruction and image analysis techniques.

The fourth part is an experimental study of the effects of aggregation of membrane proteins on the organization and polymerization of cytoskeletal elements inside cells and its relation to transmembrane signalling.

We have developed quantitative methods to analyze electronmicrographs of biological systems. The methods include digitization of micrographs and computational analysis of their contents (e.g., protein particles on membranes).

The binding of hormones to their receptors on cell membranes is believed to be the first step in their biological action. Insulin binding sites appear in groups on the plasma membranes of rat adipocytes and as separated sites on rat liver plasma membranes. These configurations are seen on electronmicrographs of these membranes using insulin bound to monomeric ferritin particles. The present study used computer analysis of the spatial distribution of these insulin binding sites and of the effects on this distribution by the disrupting agent cytochalasin B and also by cytochalasin D. This study points out that the distance between adjacent sites in a group does not seem to exceed 400 angstroms. Also, the relative change by Cytochalasin B in distribution of this insulin preparation in groups of 1, 2, and 5 or greater was not affected by the defined separation distance (at least up to 600 angstroms) used to define a group. Cytochalasin B appears to disrupt portions of groups of insulin without regard to distances between adjacent

PROJECT NUMBER 201 CT 00968-02 PSL	
PROJECT TITLE QUANTITATIVE ANALYSIS OF THE ELECTRONMICROSCOPY OF CELLS AND THEIR PLASMA MEMBRANES	
PI: N. Gershon, Ph.D., Visiting Scientist, PSL, DCRT L. Javett, M.D., S. Javett, M.D., and D. S. Schwartz, M.D., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania P. Gordon, Ph.D., Clinical Director, NIDDK J. L. Carpenter, University of Geneva, Switzerland R. Weiss, Ph.D., Chief, PSL, DCRT R. Nussli, Ph.D., PSL, DCRT A. Porter, Ph.D., University of Colorado, Boulder, Colorado B. Brown, Ph.D., NIDDK M. Winkler, Ph.D., PSL, DCRT	
PROJECT SUMMARY In this study, the distributions of insulin binding sites on the surface of rat adipocytes and liver plasma membranes were studied using monomeric ferritin-insulin viewed by electronmicroscopy and analyzed by newly developed quantitative methods. It shows that insulin binding sites are non-randomly distributed on rat adipocyte cell surfaces while they are uniformly distributed on liver plasma membranes. The quantitative characteristics of the receptor groups and the mode of action of cytochalasin B and D have been elucidated. In the second part we have been looking at the organization of intramembraneous particles on lymphocytes and coated pits on adipocyte-like fibroblasts. In the third part of this investigation, the three dimensional structure of polymerization centers for macromolecules in cells has been pursued using three-dimensional reconstruction and image analysis techniques. The fourth part is an experimental study of the effects of aggregation of membrane proteins on the organization and polymerization of cytoskeletal elements inside cells and its relation to transmembrane signalling.	

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receptor sites within a group. Computational analysis of morphological studies on insulin and other receptors should provide more information than visual analysis.

To further the understanding of insulin action, experiments are done on fibroblasts transformed into adipocyte-like cells. These cells look and respond to insulin as do adipocyte cells. Coated pits were inferred to participate in the mechanism of insulin action in some cells. We would like to study the reorganization of coated pits on membranes of cells undergoing this type of transformation and examine what the changes are in spatial distributions on the membranes during this kind of differentiation. This is part of a broader study of the membrane's structure in the undifferentiated and in adipocyte phenotype of the 3T301 cells.

A three-dimensional arrangement of some cell organelles is important to cell function. At the present time electronmicroscopy is the only method available to visualize microfilaments, microtubules, and cell membranes at sufficient resolution to study their arrangement and interrelationships. Using electron micrographs produced by the high voltage electron microscope (a national resource sponsored by NIH) in Boulder, Colorado; the new digitizing system being constructed at PSL; and the computational facilities at DCRT; the three-dimensional location of organelles in cells is being measured and their structure is going to be elucidated. This will shed light on what determines and maintains cell form in normal and malignant cells. This work is done with R. Nossal, K. Porter, B. Bowers and M. Weissberger. The method has been developed and the analysis of the data has been initiated.

Membrane proteins can interact with various components inside the cell, e.g., cytoskeletal elements. We have looked for possible physical mechanisms to account for the attachment of membrane proteins to cytoskeletal filaments, e.g., by entanglement or by polymerization of cytoskeletal elements around aggregated membrane proteins.

There are some indications, on the visible light microscopic level, that these cytoskeletal structures are affected by changes in the location of cell surface proteins. We have developed an electron microscopic method that makes it possible to observe these structures inside the cell. In order to enhance the visibility of the cytoskeletal microfilaments we use the Evans & Sutherland facilities for image display and analysis. With this method we plan to quantitate the amount and morphology of cytoskeletal elements. In doing so,

changes in the cytoskeleton will be detected and correlated with changes in cell surface proteins. These studies might shed light on how signals are transferred through membranes to cell interiors.

Keyword Descriptors: Insulin binding sites, insulin receptors, cytochalasin B, membrane proteins, electronmicroscopy, coated pits, high voltage electronmicroscopy, digitization of electronmicrographs, cell surfaces, microfilaments, cytoskeleton.

Publications:

Gershon, N.D., Smith, R.M., and Jarett, L., Computer assisted analysis of ferritin-insulin receptor sites on adipocytes and the effect of cytochalasin B on groups of insulin receptor sites. *J. Membr. Biol.* 58:155-160, 1981

Diffusion of Molecules on Cell Surfaces and Light Scattering from Fluids

A theoretical study was carried out to determine the rate of cell surface curvature on the observed diffusion rate of membrane proteins using fluorescence photobleaching recovery. For with a similar geometry to natural microvillous membranes, it was found that the assumption that the membrane is curved does not affect the calculated diffusion constant to a large extent.

In the second part, hydrodynamic equations and the light scattering spectrum from viscoelastic fluids were derived. Two cases, fluid-like and solid-like viscoelastic fluids, were studied.

A. Diffusion of Molecules on Cell Surfaces. Fluorescence photobleaching recovery (FPR) techniques have been used to study lateral movement of molecules on membranes. Fluorescent molecules within a circular spot are bleached and the time dependence of the fluorescence recovery in the spot is measured. The physical interpretation of these results in terms of diffusion along the membranes is based on the assumption that the surface is planar. However, biological membranes may be nonplanar, e.g., they may have blebs and microvilli. To study the effect of nonplanarity on the diffusion rate, the diffusion equation for motion on curved surfaces was derived. This equation was employed in studying the diffusion along a 'wavy' surface of the form $A \cos(kx) \cos(ky)$. The numerical calculations show that for $k=10$ (micrometers)⁻¹ and a bleached spot of 1 micrometers in diameter, the time dependence of the intensity of fluorescence in the bleached spot depends on A at low values of A (0, .1, and .5 micrometers) while the dependence on A at higher values of A (.5 compared with 1 and 2 micrometers) is weak. Assuming that the membrane is planar, the interpretation of FPR measurements

J. C. GILLESPIE, ACTING DIRECTOR, ECONOMIC PRODUCTION DIVISION (100-100-100-100)		ALL INFORMATION CONTAINED HEREIN IS UNCLASSIFIED DATE 10/10/01 BY 100-100-100-100		PROJECT NUMBER Z01 CT 00064-02 PSL	
TITLE: COMPUTER TYPESETTING OF SCIENTIFIC PAPERS					
DATE: October 3, 1980 to September 30, 1981					
TYPE: A. Product (and character of work)					
NAME, LABORATORY AND UNIVERSITY, OPERATIONS, AND FIELD OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT					
PI: V. A. Parsington, Ph.D., PSL, DCRT N. Crawford, Computer Assistant, PSL, DCRT M. McNeil, Computer Systems Analyst, Consultant M. Douglas, Computer Systems Analyst, LAS, DCRT M. Horton, Computer Systems Analyst, LAS, DCRT P. Miller, Information Officer, DC, DCRT J. Prewitt, Ph.D., DC, DCRT N. Fayman, Computer Specialist, CCB, DCRT J. Fayman, Computer Specialist, CCB, DCRT					
OTHERS:					
COLLABORATING UNITS (LA * 2)					
Rockefeller University Press, Science Press, Biophysical Journal, Government Printing Office, Waverly Press					
LAB(S):					
Physical Sciences Laboratory					
INSTITUTION AND LOCATION					
Division of Computer Research and Technology					
TOTAL MANHOURS: 0.6 PROFESSIONAL: 0.3 OTHER: 0.3					
OTHER APPROPRIATE DATA(S)					
(1) (a) HUMAN SUBJECTS () (b) HUMAN TISSUES () (c) METHOD					
() (d) MINORS () (e) INTERNALS					
SUMMARY OF WORK (200 WORDS OR LESS - UNLESS OTHERWISE SPECIFIED)					
The object of this project is to be able to produce magnetic tape versions of material intended for publication. These tapes can be "dumped" directly on the copy editing/typesetting computer systems of the publisher. Our method is to write programs using MIBUS files as source material that will produce magnetic tapes to the specifications of each publisher. The execution of these tape writing programs should be as simple as requesting a paper copy of the same text. Such electronic conversion of texts has been shown to be cheaper, faster and more accurate than the old way of retyping material by the publisher. Typesetting costs can be halved. Already one journal is offering a major dis- count in page charges to authors submitting "computerprints." Others should follow. The ultimate savings to the NIH are expected to be significant.					
PREPARED BY: (Name, Title)					

might yield a diffusion constant that is 40 percent (for $A=1$) of the real diffusion coefficient along the curved surface. These results suggest that the transition from a plane to a surface with small microvilli slows the diffusion process while the transition from small to large microvilli practically does not affect the diffusion rate of molecules in the bleached area.

B. Light Scattering from Microelastic Fluids.
 Viscoelastic systems, as all other macroscopic systems, can be studied by phenomenological and statistical approaches. The common phenomenological approach consists of three stages:

1. The finding of the stress-deformative structure of the system
2. The construction of differential equations of motion. [This construction usually involves some phenomenological (transport) coefficients.]
3. The carrying out of some, usually mechanical, experiments estimating values for these coefficients.

However, this scheme may not always be applied. The problem is that there is a wide class of fluid systems, namely, overcooled liquids, which do not permit (because of their instability) usual rheological experiments in order to define their structure. For such systems, nonmechanical experiments became very important.

In this work we continued the phenomenological study of the two simplest viscoelastic systems: Kelvin body (the solid-like system) and Maxwell body (the fluid-like system). We generalized and corrected the dynamical equations for these systems and calculated the vertical-horizontal (VH) spectrum of light scattered by these systems. We found that the form of these spectra can sometimes uniquely define the structure of the system.

For the solid-like system we have derived the hydrodynamic equations and the VH light scattering spectrum using a molecular approach.

Keyword Descriptors: Membrane proteins mobility, lateral diffusion, microvilli, fluorescence photobleaching recovery, light scattering, hydrodynamic equations, viscoelastic fluids.

Publications:

Aizenbud, B. M., and Gershon, N.D.: Hydrodynamic equations and VH light scattering from viscoelastic (solid-like and fluid-like) systems. Phenomenological approach. *Physica A* (in press).

Computerized Typesetting of Scientific Papers

The object of this project is to be able to produce magnetic tape versions of material intended for publication. Those tapes can be 'hung' directly on the copy editing/typesetting computer systems of the publisher.

Our method is to write programs using WYLBUR files as source material that will produce magnetic tapes to the specifications of each publisher. The execution of these tape writing programs should be as simple as requesting a paper copy of the same text.

Such electronic conversion of texts has been shown to be cheaper, faster, and more accurate than the old way of retyping material by the publisher. Typesetting costs can be halved. Already one journal is offering a major discount in page charges to authors submitting 'compuscripts.' Others should follow. The ultimate savings to NIH are expected to be significant.

It has been shown that the texts of many if not most of the scientific papers produced on magnetic memory typewriters ('word processors') at NIH can be transferred into the WYLBUR system. Many papers are also keyed directly into WYLBUR. A program by Bonnie Douglas and Martha Horton is being used and improved by Nancy Crawford to produce magnetic tape records of such texts. These tapes are then suitable for text conversion electronically to typeset galleys without retyping manuscripts.

Our early success in producing a paper (by John Fletcher, LAS/DCRT) in this way has led to an agreement with the Biophysical Society, its publisher Rockefeller University Press, and its printer Science Press, to supply us with magnetic discs, cards or tapes of papers for experimentation. The object here is to obtain material in order to learn to transfer various forms of magnetic record into the WYLBUR system and then to produce typesetter-ready magnetic tapes from WYLBUR.

The original tape writing program is being transferred by M. McNeel from the PDP-10 system to the IBM 370 system to allow direct writing of tapes using WYLBUR command procedures. Features of the new WYLBUR system are being incorporated to allow far more efficient tape writing. The tape writing program is being generalized to prepare material for other publishers. Initial experiments have been performed by Waverly Press under the auspices of the *Journal of Biological Chemistry* and a new collaboration is being established with the Computer Society.

With the automatic conversion of texts that would otherwise be laboriously retyped and with the likelihood that publishers' copy editing can now be done at a terminal rather than on paper copy, the new system provides speed, accuracy and cost savings. Consequent reduction in page charges is already a fact with the *Biophysical Journal*. Other journals appear ready to grant similar reductions when similar procedures are available.

Keyword Descriptors: computer typesetting, WYLBUR, computerized composition, magnetic tape, floppy disc, magnetic card, compuscripts.

Publications: None.

Data Management Branch

J. Emmett Ward, Chief

Summary of Activities

Clinical Information Utility (CIU). Clinical Support Section (DMB). This ongoing major effort maintains a data base for research and patient care in the NIH Clinical Center. During this past fiscal year a number of improvements were made: the Surgical Pathology subsystem and database were fully implemented using the SNOF System to encode the diagnoses; the general design of an integrated database was completed; a subsystem was defined, designed, and implemented for purging cumulative laboratory data from the weekly production runs; software was developed for producing final cumulative laboratory summaries; several modifications were made to the CIU that reduce the run and connect times for producing the weekly laboratory summaries and updating the databases; and a subsystem was designed to preprocess clinical laboratory data for the integrated database.

Combined Cardiology/Heart Surgery Data System. Larry Martin (DMB/ASPS); Roger Dailey (DMB/DBAS); C. McIntosh (NHLBI); D. Rosing (NHLBI). This combined system provides a chronological record of the medical activity of NHLBI Cardiology and Heart Surgery Branch patients. In FY81 effort was directed toward meeting the routine and ad hoc reporting requirements and new statistical needs of the NHLBI physicians and researchers and the system was expanded to include nuclear angiogram information. An online private disk was assigned to the project during the year to improve data query and analysis response time.

Pulmonary Function Data System. Judy Mahaffey (DMB/ASPS); Ronald Crystal (NHLBI/IRPB); Larry Nadel (DCRT/CSL). The Pulmonary Branch of NHLBI has requested the development of a combined computerized data base for pulmonary function and exercise testing data to replace existing separate ones. It is planned that the system will interface a NOVA and an LSI-11 minicomputer. This year analysis was completed and a design proposal was prepared during the last year.

Analysis of SLE Nephritis Patients. George Shakarji (DMB/OC); John H. Klippel (NIADDK); John Decker (NIADDK). The storage phase of the development and implementation of this ongoing project is now completed with major modifications included. The system has the capability of storing and retrieving chemistry and therapy data on all SLE (Systemic Lupus Erythematosus) nephritis patients. Data on a subset of SLE patients, participating in the immunosuppressive trials and assigned to receive either prednisone only or the combination of prednisone and cyclophosphamide, are now being studied to evaluate certain chemistry constituents.

Multivariate and Univariate Forecasts for Blood Constituents. George Shakarji (DMB/OC); Eugene K. Harris (DCRT/LAS). This study, which is part of continuing studies on variability of blood chemicals in normal people, uses data compiled through the health maintenance program in Japan. The database includes 15 to 18 semiannual values for 6 biochemical tests in over 16,000 men and women between the ages of 20 and 70. Programming for this study involved univariate and multivariate time series systems. Programs were completed to compute homeostatic and random walk (non-stationary) models for both the univariate and multivariate analyses. All of the methodologies were applied to the database to compute and compare results and predictions.

Psychobiology Patient Information System. Dennis George (DMB/ASPS); Steve Soroka (DMB/ASPS); Frank Putnam (NIMH/BP). The purpose of this project is to condense a large amount of data for a small number of patients studied by the Biochemical Psychiatry Branch into a format that is useful for research analysis. During the last year analysis was completed and a design proposal was submitted for a system that extracts and reformats data from the Clinical Information Utility for analysis by existing statistical packages.

Dyslipidemia Computerized Recordkeeping System. George Roberts (DMB/SAS); Ernst

Schaefer (NHLBI/MD). This system keeps records on clinical laboratory data for normal and dyslipidemic subjects and provides for routine reporting as well as for ad hoc queries and preparation of selected subfiles for statistical analysis. An individual history report program was supplied during FY81. For current reporting requests, the new SAS online graphics package was used.

BRIGHT Augmentation. Brian Cole (DMB/SAS); David Rodbard (NICHD/BES); Jay Shapiro (CC). A computer system is being developed on the DECsystem-10 that will enable Clinical Center investigators to analyze their own clinical data. Available thus far are a t-test module and a plotting module. Also to be included are descriptive statistics, chi-square test, linear regression, ANOVA, normality test, non-parametric tests, and life table analysis. Modules are to be added as requested by investigators.

Diet Composition/Menus. Diane Feskanich (DMB/SAS); Dennis Sprecher (NHLBI). This is a system for determining the nutritional profiles of patient menus. With appropriate modifications, the 'MR FIT' nutritional coding tape and diet composition programs were made operational at NIH. An input module for Dyslipidemia patients' dietary records has been supplied.

Survival System. Diane Feskanich (DMB/SAS); Ardyce Asire (NCI). This life table analysis system was originally developed in the 1960's to support the End Results in Cancer studies of NCI. Maintenance and improvement of the system is now the primary goal. During FY81 the system was sent to: Rhode Island Health Services Research, Inc.; Department of Health, San Juan, Puerto Rico; and Rosewell Park Memorial Institute, Dept. of Health, Buffalo, NY.

Prevalence of Major Neurological Diseases--Nigeria. Joe Huston, Mary Lee Dante (DMB/SAS); Bruce Schoenberg (NINCDS/NS); Dr. Osuntokun (University of Ibadan). This WHO-sponsored study consists of four parts: census and health screen, evaluation of risk factors, neurological exam results, and follow-up. A pilot study was done to determine validity and usefulness of the questions and worth of the questionnaire. Processing of these pilot forms led to many suggestions for improving the study protocol and questionnaire format.

Neurological Screening Summary. Brian Cole (DMB/SAS); B. Schoenberg, D. Anderson (NINCDS/NS). A survey of neurological disorders was made in a Mississippi county; this study examines the epilepsy, stroke, psychomotor delay/cerebral palsy, transient ischemic attacks, and Parkinson's Disease

data. Extensive validity checks and consistency editing were required. Preliminary analysis of Parkinson's Disease, including frequency tables and bar graphs, has been supplied.

Seroepidemiology Data Processing System. Judy Mahaffey (DMB/ASPS); Paul Levine (NCI). The Clinical Studies Section, NCI Laboratory of Viral Carcinogenesis, is trying to find characteristics of serum samples that can be used to predict cancer. To this end, a computer system has been designed to manage all data necessary for efficient inventory control, test results feedback, and statistical analysis. The system is now operational and reports from the system are being sent to collaborating scientists in the U.S., Ghana, Greenland, and Singapore. During the past year a new contractor took over the the running of this system, and was provided with assistance in setting up to correctly run the system.

Idiopathic Hypereosinophilic Syndrome Protocol. Brian Cole (DMB/SAS); John Harley (NIAID). A data base is being set up that will allow easy storage, retrieval, and analysis of a large amount of data that has been paper-collected on hypereosinophilic patients since 1967. Information drawn from the CIU will be included. In FY81 drug therapy information was extracted from the CIU and patient response patterns studied.

Physiologic and Behavioral Responses to Apomorphine. Diane Feskanich (DMB/SAS); Neal Cutler (NIMH). The effects of apomorphine on physiological and psychological variables are being studied in groups of patients and volunteers, male and female. Graphs have been run on time of peak hypothermal response, mean duration of the response, and time of rebound by age, sex, and other variables. Also being examined is the development of brain tolerance to the drug.

Smithsonian Tick Collection Query/Retrieval System. Diane Feskanich (DMB/SAS); Carleton Clifford, Jim Kearins (NIAID/RML). The Rocky Mountain Lab has catalogued its tick collection on tape and sent the data to the Smithsonian Institution. DMB is supplying the ability to query this file from Montana using the DCRT central computer facilities. During FY81 Ms. Feskanich assisted RML in the selection of a DataPoint word processor for installation in Montana, and ensured that the software would interface with DCRT software. Ms. Feskanich has provided interactive DataPoint programs for data entry and query/report and will be training RML personnel in use of the word processor when it is installed.

Monkey Management System. Diane Feskanich

(DMB/SAS); Robert Williams (NICHD/ERRB). A data base is being developed of bibliographic and medical information, plus the experimental history of each monkey in a colony of 500 to 1,000 monkeys, with a turnover of 300 each year. The system will be used to select appropriate individuals for specific experiments, and to prepare daily work assignments for caretakers and technicians.

Musculoskeletal Model. Sig Knisley (DMB/SAS); Richard Lynn (NIADDK/ABSDP). This is a study of the structure of live muscle fibers as they contract. From a model, diffraction patterns will be computed and compared with real diffraction patterns produced by living muscle fibers. During FY81 myosin data has been processed with the PDP-10, linked with the PDP-11, and put up on the Evans and Sutherland picture system and the frame buffer for 3-D conformational analysis and manipulation.

Wild Mouse Breeding Colony Data Processing System. Vivian Pelham (DMB/ASPS); Ernest Plata (NCI). The Laboratory of Viral Carcinogenesis, NCI Division of Cancer Cause and Prevention, breeds and raises a rare and valuable strain of wild Asian mice originally acquired from Vietnam. A system that will maintain all data collected on these animals and aid in selective breeding, carcinogenesis studies, aging studies, etc., was completed during the past year.

Canine Breeding Colony Data Processing System. Peter Basa (DMB/DBAS); Dennis George (DMB/ASPS); T. Woffle (DRS/VRB/ACS). The goal of this project was to develop a system to assist the Veterinary Resources Branch, DRS, with its record keeping and work scheduling. The system is complete. DRS is now in the process of installing a word processing system (CADO) in Poolesville to handle all data entry, maintenance, etc. When this is complete, DMB will work on interfacing the two systems.

Strain Specificities Reference System. Steve Soroka (DMB/ASPS); David Sachs (NCI). A computer system is being developed for the Division of Cancer Biology and Diagnosis, NCI Immunology Branch, to assist in transplantation biology research. The system will be used to help locate existing cogenetic mouse strain products and/or to design mouse strain products with specific antigens that are used in experiments relative to the development of sera. Analysis was completed and a design proposal was prepared during the past year.

Ectromelia Epidemiologic Survey. Dennis George (DMB/ASPS); Gordon Wallace (NIAID). This project provides the data processing services necessary to

determine the environmental factors that most likely contribute to the spread of Ectromelia (Mouse Pox). The project was completed during the past year. Using the results from the study, Dr. Wallace wrote a paper, which he presented at a National Conference on Lab Animal Diseases in October, 1980.

Estimating Q Matrix in the Kalman Recursion. George Shakarji (DMB/OC); Eugene Harris (DCRT/LAS). A package has been implemented that would estimate the matrix of 'shift' variances and covariances, or the Q matrix. The package assumes either that Q is unknown, in which case the weight function and the matrix of predicted values can be calculated directly, or that Q is unknown but that the series of observations is long.

Multivariate Time Series Packages. George Shakarji (DMB/OC); Eugene Harris (DCRT/LAS). Two packages that would input multivariate observation vectors of related tests were completed and tested. The homeostatic approach assumes the existence of a constant set point about which the serial measurements fluctuate; successive observation vectors are presumed to be mutually independent. The non-stationary, random walk approach does not assume any constant homeostatic subpoint. It postulates instead that the true value at any time is shifted randomly from a previous time. In this procedure the predicted value is a weighted (exponentially smoothed) average of past results.

Materiel Management System (MMS). Marvin Katz, Ron Wicks (DMB). This ongoing administrative project utilizes data base technology in support of NIH-wide procurement, receiving, and payment activities. As the MMS entered its fourth year of development and operation, much time was spent in enhancing existing software. During FY81 some 50 change control items successfully went into production. New developmental efforts implemented were:

1. Provision of a delegated interface to MMS for the B/I/D's Administrative Offices. This interface includes: procurement entry at point of origin, receipt of entry, and online review and control of all pertinent data by the Administrative Office. This feature will be phased into the B/I/D's as terminals become available.

2. Development of a new numbering system for the delegated procurement actions that originate in the B/I/D's.

3. Streamlining of DFM Accounts Payable functions by automatic voucher generation as part of the Treasury schedule preparation.

4. Development and implementation of an invoice entry subsystem for DFM.

5. Completion of subsystem design for a stock inventory subsystem.

6. Cutover to production of a source subsystem that allows blanket purchase agreements and indefinite delivery contracts to control telephone charge order and record of call validity.

Requirements Analysis for Financial Management Data Base. Clare Hoover, Jeff Schriver (DMB/DBECS); Harry Hsu (SIMCOM/USAF). As an adjunct to the full statement of Division of Financial Management accounting requirements, the study participants: developed a complete structured flow chart of the existing Central Accounting System (CAS); defined the detailed flow of key CAS transactions; and created a matrix of all transactions, master files, and their processing relationships. These documents will be used as the basis for evaluating vendor accounting packages.

General Support for Central Accounting System.

Clare Hoover, John Price, Jeff Schriver (DMB/DBECS). During the fiscal year, the Data Base Enhancement and Control Section developed enhancements and new programs, and conducted studies for, the Central Accounting System. Because this support involved almost 80 separate projects of varying size, they will not be enumerated here.

Performance Index/Grant Awardees. Mary Lee Dante (DMB/SAS); William Parker (NINCDS/EAP). Under study is a system for tracking K07, K04, and F32 applicants. To do this, information must be acquired from the IMPAC and CRISP files, organized (by category, principal investigator, and grant), and printed in matrix format. If pursued, this can be generalized for other requests.

DRR Grants Subproject System. Vivian Pelham (DMB/ASPS); Jean Babb (DRR). The existing DRR Grants Subproject System, which uses Conversation Programming System, is being evaluated. A proposal was made for the redesign of this system to make use of more current, supportable technology. The proposal was accepted and the system currently is being developed.

NIH Nutrition Grants Monitoring System. Judy Mahaffey (DMB/ASPS); Thomas Vogl (OD). A system has been designed for the NIH Nutrition Coordinating Committee to assist them in monitoring and reporting data on biomedical and behavioral nutrition research at NIH and at other agencies within DHHS. The system is operational and Dr.

Vogl's office is currently using it to answer inquiries--from NIH Directors' offices, the White House, Congress, and the public--that relate to dollar amounts and percentages of grant money being spent in the area of nutrition.

Review and Evaluation Branch Grants

Information System. Penny Brogan (DMB/ASPS); Harry Canter (NCI). The computerized Research Analysis and Evaluation Branch Grants Information System, a highly specialized grants management system, was designed and implemented for the Division of Cancer Grants, NCI. Enhancements are currently being made to the Intramural and Funded Grants subsystems, and the system is being extended to include contract data. In the future, a Training Grants system will be developed and history file maintenance will be added to the Intramural projects and unfunded grants systems.

NIH International Activities and Personnel

Monitoring System. Penny Brogan (DMB/ASPS); Libby Low (FIC). A system has been developed to process financial and visa data on the foreign guest workers and foreign visitors at NIH. The Fogarty International Center is currently using this system to provide reports for the Visiting Program, for foreign nationals, and for foreign embassies. The growth of the current data files will necessitate a future revision of the system to separate current data from historic data. During the past year an analysis of all FIC requirements was completed and a design proposal with recommendations for improving their system was prepared.

Committee on Academic Science and

Engineering (CASE) Reports. Darius Georg (DMB/ASPS); J. Bailey (OD/OPPE). This project involves a broad spectrum of data processing support required for the collection and reporting of DHHS obligations to institutes of higher education, research and development centers, and non-profit institutions. This is an ongoing project.

MMS Query and Reports. Jane Blessley (DMB/ASPS); Joe Campbell (DMB/DBAS). This project provides an economical method for the selection and reporting of data from the NIH Administrative Data Base. Ms. Blessley provides recurring and ad hoc reports from the data base for all segments of the NIH community.

System for Statistical Complaints of

Discrimination at NIH. Darius Georg (DMB/ASPS); G. Yee (OD/DEO); M. Williams (OD/DEO). This project establishes and maintains a file that provides statistical data, on a case by case basis, of formal and informal complaints of discrimination at NIH. In

the past year Mr. Georg revised and simplified the retrieval process.

ARMS/TDCS Interface. Dennis George (DMB/ASPS); B. Hughes (OPA/P); A. Amatucci (OA/M). This project is intended to create an NIH Personnel System that is a composite of the current NIH personnel system (ARMS) and the DHHS Personnel System (TDCS). In the past year the analysis and design of the proposed system was completed. The ARMS Steering Committee has approved the proposal and the system is presently being implemented.

Radiation Safety Control System. Charles Twigg (DMB/ASPS); R. Zoon (DRS/RSB). This system is designed to monitor the use and users of radioactive isotopes at NIH. When complete, this system will include five subsystems: inventory and bioassay, lab survey and airborne release, waste processed and activity balance, training, and film badges. In the past year extensions were made to the inventory and bioassay subsystems to satisfy Nuclear Regulatory Commission requirements. Development of the lab survey and airborne release subsystem was begun. All subsystems have been completed except the waste processed and lab survey.

Electrical Safety Program System. Larry Martin (DMB/ASPS); Steve Soroka (DMB/ASPS); Howard Metz (DRS/BEIB). The chief of Scientific Equipment Services of the Biomedical Engineering and Instrumentation Branch has requested a system to help monitor maintenance of equipment at the Clinical Center. A system is being designed to computerize the results of routine electrical safety checks and preventive maintenance performed on hospital equipment. The system will be used by DRS to schedule equipment checks, to provide reviews on instruments checked by contractors and by the CC, and to provide statistical information on different types and repair histories of equipment. A design proposal has been accepted, and the system is currently being implemented.

Design Billing System. Peter Basa (DMB/ASPS); Robert Weymouth (DRS/OD). This project converts the manual accounting system for the Design Unit in MAPB/DRS to a computerized system. Analysis, design, and development of the system were completed during this year.

Information System of Extramural Scientists. Darius Georg (DMB/ASPS); William Rhode (OD/OPPE). This system creates a data base of information drawn from various sources in order to perform analysis of various patterns of involvement in NIH science review activities by extramural

scientists. The data base was created during the year and reports are being run as requested.

Medical Records Auditing System. Judy Mahaffey (DMB/ASPS); Gloria Burich (CC/MRD). The purpose of this system is to assist Medical Records in the monitoring and reporting of the status of medical records from the time they enter the department until they leave. When the system is developed, it should replace four manual systems now being used by the Medical Records Department. During the past year analysis was completed and a proposal was submitted. The proposal has been accepted, and the system is currently being implemented.

Correspondence Control System. Steve Soroka (DMB/ASPS); Dennis George (DMB/ASPS); Zaven Khachaturian (NIA/OD). The objective of this system is to monitor the status of staff assignments and correspondence assigned to NIA for processing and review, and to provide a query facility that will allow NIA personnel to locate correspondence (old and current) pertaining to a current issue or problem. During the last year analysis was completed and a design proposal was submitted for approval.

AIRS Personnel System. Vivian Pelham (DMB/ASPS); L. Lee Manuel (DCRT/OD). This project involved a complete revision of this system due to the discontinuation by CCB of the Conversation Programming System. Analysis, design, and implementation were completed during this year.

HMO Label Programs. George Roberts (DMB/SAS); Lois Eberhart (OHMO/OPS). The Office of Health Maintenance Organizations maintains several address lists. They were provided with an interactive updating capability, a number of reports, and a gummed label option.

Space Management System. George Roberts (DMB/SAS). This system provides a method whereby the Office of Research Services can keep track of all space in all buildings occupied by NIH. The Fort Dietrick facility was added to this system during FY81.

Chinese Personalities and Institutions in Biomedicine. Judy Mahaffey (DMB/ASPS); Joseph Quinn (FIC); Joseph Lee (FIC). International exchanges in the field of biomedicine between the U.S. and the People's Republic of China have increased rapidly. The Fogarty International Center has requested DMB services to design a system for the computerization of data on biomedical scientists and institutions in the PRC. The system will be used by the FIC officials in briefing NIH and non-NIH scientists interested in biomedical research in China.

During the year, analysis was completed and a design proposal was submitted to FIC.

Selective Dissemination of Information. Sig Knisley (DMB/SAS). SAS has continued its support of the current awareness search for both Chemical Biological Activities (CBAC) and Biosciences Information System (BIOSIS). Retrospective searches are referred to the NIH Library staff.

Sickle Cell Disease, Health/Science Seminar Evaluation. George Roberts (DMB/SAS); Katrina Johnson (NHLBI/SCDB). A battery of tests probing general knowledge of Sickle Cell Disease is given to groups of teachers prior to a two-day seminar on the disease. Then a post-test is given to measure the value of the seminar. Some analysis was done on a set of tests already scored, mainly for the purpose of evaluating the test questions. Advice also was provided during the process of requesting proposals from contractors for administering the program.

SLANG (Structured Language) Compiler. Bob Magnuson (DMB/OC). SLANG is designed to assist programmers to generate block structured assembly language code on the IBM system 370. The features added include automatic indentation, generic statement numbering, boxed comments, and program structure display.

Voice Input and Synthesis Support. Bob Magnuson (DMB/OC). As a follow-up to DMB's initial voice input project, this section is examining the feasibility of developing voice input/output applications by way of microprocessors, which can act alone or as front end processors to larger computers. This year was spent modifying the design of a microsystem with plug-in peripherals, purchasing some hardware, and providing appropriate software.

SFOR (Structured FORTRAN) Compiler. Bob Magnuson (DMB/OC). Designed to assist programmers writing structured programs, the SFOR compiler generates block-structured IBM FORTRAN source code. There are six different kinds of blocks available to the FORTRAN programmer--CASENTRY, FOR, IF, LOOP, REPEAT, and WHILE.

RMAG Products Support. R. Magnuson (DMB/OC). Necessary support is provided for RMAG, SLR, Logic Subroutines, Arithmetic Subroutine, SLANG, REFORMATGEN, REPORTGEN, TRANSACTGEN, Standardized Update, Voice Input, and SFOR. This ongoing support includes software maintenance, customer assistance, and the teaching of formal DCRT courses on these products. In particular, a special effort had to be mounted to change over to the new WYLBUR format data sets.

Computer Center Branch

Joseph D. Naughton, Chief

Summary of Activities

New Languages. An entirely new version of WYLBUR, designed and implemented by the Center over the past several years, was made operational in a full production mode in early January. In addition to retaining all the capabilities of the previous version, the new version provides many new functions including document formatting, pattern matching, catalogue and PDS support, session recovery, and command procedures (EXEC files), plus many enhancements to existing facilities. The new version uses much less CPU time than its predecessor at the same level of user load and can accommodate many more simultaneous users.

SPEAKEASY, a computing language for scientific and mathematical problem solving, became available under TSO on the System 370. Developed by a physicist at the Argonne National Laboratory, SPEAKEASY provides a quick and simple means of formulating mathematical problems and obtaining results. The language contains over 500 functions and commands that perform matrix and array operations, numerical differentiation and integration, statistics, and character processing. Because its notation and syntax are similar to those used in mathematics, it provides extensive new scientific and mathematical capabilities without burdening the user with the details often inherent in computer programming. SPEAKEASY may be self-taught at NIH through two online facilities; TUTORIAL and HELP.

The IBM PASCAL/VS Compiler was tested and installed on the System 370, and is available for interactive use under TSO or for batch processing. PASCAL is a relatively small but very powerful language that has become widely used throughout the data processing industry. It is a very concise language with few defaults or implicit conversions, making it easy to use. The PASCAL/VS compiler contains many extensions to the International Standards Organization proposed PASCAL standard. It provides the ability to divide programs into separately compilable sections, a debugging facility,

and numerous other features.

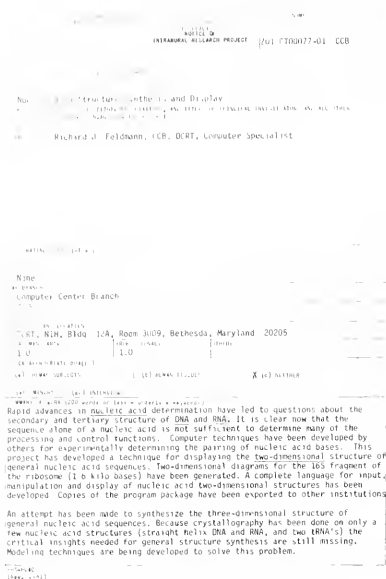
The Conversational Programming System (CPS), the first interactive programming facility offered at NIH, was replaced by the more modern VS BASIC, an improved version offering many features not previously available. Guidelines were developed to assist users in converting CPS-PL/I programs to use the PL/I Optimizing Compiler under TSO. The command procedures facility of WYLBUR provided a viable mechanism for rewriting some programs.

New Software. Two powerful new graphics packages were made available on the IBM System 370. TELL-A-GRAF, an interactive system that uses conversational commands, may be used to create a variety of graphs and charts. The system is easy to learn and does not require programming experience. The other program, DISSPLA, is a library of subroutines that can be called by the user's program. Although some programming experience is necessary, DISSPLA is also easy to use and enables the user to integrate data analysis and graphical display into a single program. Both TELL-A-GRAF and DISSPLA are capable of driving a wide variety of graphics devices.

A new software package was installed to assist users in the diagnosis of program abends that cause dumps. ABEND-AID analyzes program abends, extracts diagnostic information, and presents the results in a few easy to understand pages. This enables users to analyze abends without having to go through the painstaking process of interpreting a dump.

Output Facilities. The OMNIGRAPH package was enhanced by the implementation of a library of 1,377 different alphabetic and graphic characters known as Hershey's fonts. These high quality, esthetically pleasing characters and symbols, manually digitized by Dr. Allen V. Hershey of the Naval Weapons Laboratory, greatly enhanced the appearance of graphs and plots generated by OMNIGRAPH and MLAB users.

All standard output forms provided by the Computer



Center were made directly available through JES2, the component of the Operating System that handles printer/punch output. This change eliminated the need for creating and processing a SPOUT tape, thereby reducing the overhead and cost for creating output at the NIH Computer Utility, and provided the ability to examine, reroute, locate the output of a job during any stage of its processing. By reducing operator involvement, the possibility of error was also decreased and turnaround was improved. An easier mechanism for users who require printed labels was developed. Each of the 21 different types of standard labels is now identified with a simple four-character name and an appropriate carriage control loop is automatically requested by JES2.

Communications Improvements. The link between the DECsystem-10 and IBM System 370 was strengthened by the addition of a second communication line between the two systems. This doubled the capacity of the link and ensured that jobs get through quickly. In addition, the effective speed of the link was further increased by several software improvements, nearly doubling the speed of transmission on each communication line.

Documentation/Publications. Publications by the Computer Center are oriented toward familiarizing users of the Computer Utility with the computer services, languages, and training available. Ten new publications and ten revised or updated titles were released this year.

Over 1,200 pages of documentation were prepared for the new version of WYLBUR, including a *Fundamentals* manual and four additional manuals on document formatting, command procedures, batch processing, and general editing. Other documentation included a *Master Index*; two reference handbooks to give the syntax of the language in concise form; and a special edition of *INTERFACE*, the Computer Center's technical notes, which introduced the new version in considerable detail and described specific differences between the new version and the old.

Seven editions of *INTERFACE* including the special WYLBUR edition and the Annual Index were issued this year. Two new features were added, 'WYLBUR Wisdom' and 'MLAB NOTEBOOK.' *INTERFACE* also ran a five part series written by Dr. Benes L. Trus, Computer Systems Laboratory, describing various techniques of scientific image processing using the Center's Surface Display System.

User Training and Assistance. Seven new lecture courses were added to the Computer Center training program this year, including 'Managing and Processing Data Sets at NIH,' 'Dynamic Biological Stimulation,' and 'BRIGHT--A System for the Creation and Use of Data Tables.' The popular WYBLUR introductory course was divided into two courses, one focusing on secretarial applications and the other on data processing applications. New seminars this year included 'Introduction to Scientific Data Analysis at NIH,' 'IMSL: International Mathematical and Statistical Library,' and 'Graphical Representation of Multivariate Data.' There were 71 sessions of 41 different classroom courses given to over 1,600 students during the year.

Self-study courses, involving either programmed instruction, workbook, audiovisual, or computer-assisted learning, continued to be popular. 'PL/I Programming,' a new independent study program written by IBM, was added to the roster this year.

Programmer Trouble Reports (PTR's) researched and answered during the year numbered 2,745. User Services applied over 4,000 system software fixes during the year and installed 14 new releases of current software packages. There were 23,000 calls or visits by users for assistance during the years.

Research Projects

In addition to the many activities, services, and facilities for NIH, the Computer Center Branch serves biomedical computing with its research work. The DECsystem-10 and the molecular graphics systems have been used to develop techniques for creating and displaying two- and three-dimensions of genetic control molecules. It is now clear that both DNA and RNA fold up into complex structures. Algorithms have been developed to create reasonable folding patterns for rather long nucleic acid sequences. A two-dimensional display algorithm has been developed to layout many of these complex structures. Using the layout algorithm it is possible to study the dynamics of the folding process by making movies. By understanding the dynamics of folding, it may be possible to understand how processing and gene control function.

Nucleic Acid Structure Synthesis and Display

Rapid advances in nucleic acid determination have led to questions about the secondary and tertiary structure of DNA and RNA. It is clear now that the sequence alone of a nucleic acid is not sufficient to determine many of the processing and control functions. Computer techniques have been

developed by others for experimentally determining the pairing of nucleic acid bases. This project has developed a technique for displaying the two-dimensional structure of general nucleic acid sequences. Two-dimensional diagrams for the 16S fragment of the ribosome (1.6 kilo bases) have been generated. A complete language has been developed for input, manipulation and display of nucleic acid two-dimensional structures. Copies of the program package have been exported to other institutions.

An attempt has been made to synthesize the three-dimensional structure of general nucleic acid sequences. Because crystallography has been done on only a few nucleic acid structures (straight helix DNA and RNA, and two tRNA's) the critical insights needed for general structure synthesis are still missing. Modeling techniques are being developed to solve this problem.

Arnold W. Pratt, M.D.

Summary of Activities

Library Automation. E. Chu; J. Mahaffey (DMB); J. Knight (CSL). In conjunction with other DCRT staff, the DCRT Librarian applies computer techniques to DCRT needs, advises other libraries, and maintains knowledge of work done outside NIH. (Details of activity in FY81 appear in Volume I of the Annual Report.)

DCRT Publication File. P. O. Miller; R. Baxter (DMB). In FY79 the Information Office began to create a file of citations for all papers published by DCRT authors. In FY81 additional work was done to correct errors in the file.

Text-to-tape Copy Preparation. P. O. Miller. This project is an offshoot of work begun in 1979 as part of a joint PSL/LAS/OD effort. In FY81, a JCL was written for creating a WYLBUR tape to drive GPO typesetting equipment. Documentation was begun in an effort to make the technique available to all NIH Information Offices.

DCRT Communications Program. P. O. Miller; W. C. Mohler. Previously called the DCRT Information Program, this is an ongoing project to develop improved and coordinated communication techniques to support DCRT activities. It has four parts: Analyzing Needs, Creating and Evaluating Products, Developing Resources, and Education. In FY81 work continued on developing and distributing information products, including a videotape about computer terminals to aid handicapped programmers and a slide show about DCRT work.

Who at NIH uses DCRT for what? W. C. Mohler; L. L. Manuel. DCRT services support activities throughout NIH for more than 3,000 registered users on some 1,100 accounts. A survey in FY79 and FY80 asked users to categorize the types of NIH activities supported by each account in the previous year. The FY81 survey in conjunction with the PAS account update confirmed previously observed difficulties in obtaining consistent and usable information by this collection mechanism. The project was stopped.

Clinical Data Management and Analysis. W. C. Mohler; B. Cole (DMB); D. Rodbard (NICHD); J. R. Shapiro (Clinical Center). In spite of the rapid growth in use of data management and statistical packages provided for NIH scientists on DCRT computers, there is a perceived need for facilities that would be easier to learn and use in NIH clinical research projects. In FY81 work began using BRIGHT, a table-oriented data management/analysis package on the DECsystem-10, developing added data analysis and display programs and exploring their usefulness for a few NIH clinicians on data sets from the Clinical Information Utility.

Multi-function Microprocessor Interface. A. W. Pratt; D. Songco (CSL). The project begun in FY80 seeks to adapt a variety of information acquisition techniques on a single microcomputer as a versatile data input/output interface for biomedical scientists and clinicians.

Medical Linguistics. A. W. Pratt, et al. This is a long-term project to define a set of semantic and syntactic forms that can aid in the analysis and interpretation of written medical statements.

Image Processing, Decision Analysis, and Computer Architectures. J. M. S. Prewitt. (Summaries for projects in this group of activities were not available in FY81.)

Research Projects

PROJECT NAME, LEVEL OF OPERATION, STATUS, CLASSIFICATION, & PROJECT NUMBER (SEE 402 FOR THIS AGENCY) PROJECT, SECURITY, AND MILITARY STATUS

PERIOD COVERED

TITLE & PROJECT (NO CHARACTER OR TAG)

October 1, 1980 to September 30, 1981

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Final-to-Late Copy Preparation

PERSONNEL, EQUIPMENT AND FACILITIES OPERATING, AND OTHER, & PRINCIPAL INVESTIGATION AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT

Patricia O. Miller, Information Officer, OD, DCRT

GOVERNANCE UNIT, (if any)

GOVERNANCE

SECTION

INSTITUTION AND LOCATION

TITLE, NUMBER, & DATE

DATE APPROXIMATE BUDGET

(a) HUMAN SUBJECTS

(b) WITHIN

(c) OUTSIDE

NUMBER OF WORDS (100 words or less - under 100 words)

Government Printing Office, Computer Center Branch

Office of the Director

Information Office, DCRT

Division of Computer Research and Technology

0.1

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(4) - 1000

Government public affairs offices have long been using word processing and text editing systems to prepare documents. These systems enable articles to be stored and later retrieved for correction and update, saving complete retyping. Once text is recorded in a magnetic medium (word processing diskettes or computer tape reels) there is another time- and cost-saving advantage - it can be furnished to a typesetter in that fashion - Editors merely insert special characters into the text, these codes instruct the typesetter's equipment to produce camera-ready copy in the specified format. This totally eliminates the galley proofreading step in print production.

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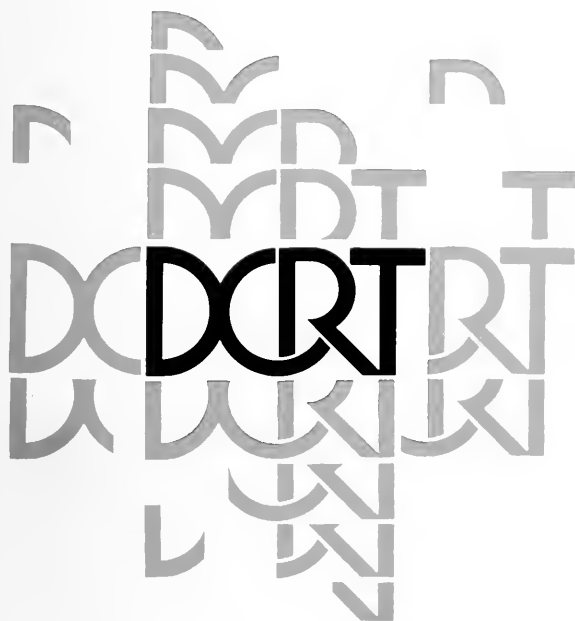
Division of Computer Research and Technology
National Institutes of Health
Bethesda, Maryland 20205

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

FISCAL
YEAR
1982

ANNUAL
REPORT

VOLUME 1



Foreword

The Division of Computer Research and Technology has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH. DCRT serves as a scientific and technological resource for other parts of PHS, and for other Federal organizations with biomedical and statistical computing needs.

DCRT programs focus on three primary activities: conducting research, developing computer systems, and providing computer facilities.

The fiscal year 1982 annual report describes our work in two volumes:

Volume 1 gives an overview of the work of each group, highlighting the year's accomplishments;

Volume 2 gives details about the projects and activities of each group.



From the Director

I am pleased to submit this Annual Report for the Division of Computer Research and Technology. It serves to remind all of us of the extent and breadth of subject matter involved in the conduct and management of the NIH biomedical research program. Biomedical computing has matured and become another essential element of the scientific excellence of NIH.

One has to be aware of increasing involvement and contributions of applied mathematics, statistics, engineering, and computer science across all biomedical research. The following examples, limited only to clinical medicine, serve to illustrate how DCRT makes these several disciplines productive throughout NIH.

The Computer Systems Laboratory is broadly involved in both the laboratory and clinical research programs in many Institutes and several Departments of the Clinical Center. Current clinical work includes:

- The Radiation Therapy System with the Radiation Oncology Branch of the National Cancer Institute,
- Automated systems for the Pulmonary Branch of the National Heart, Lung, and Blood Institute,
- The Positron Emission Tomography Facility, the focus of exciting collaborative projects among staff of the National Institute on Aging and the National Institute of Neurological and Communicative Disorders and Stroke, and
- Other projects in the Medical Intensive Care Unit, Electrocardiography/Heart Station, and Anesthesiology Service of the Clinical Center and its Departments of Clinical Pathology, Nuclear Medicine, and Rehabilitation Medicine.

The Laboratory of Applied Studies has been active in a variety of clinical research projects. Many of these have been collaborations with users of the systems designed by CSL. Areas of activity currently include laboratory medicine, electrocardiography, and pulmonary medicine.

The Laboratory of Statistical and Mathematical Methodology provides mathematical tools and consultation for clinicians from all Institutes. In addition, it too has collaborative projects with medical scientists. Even the Physical Sciences Laboratory, with its major focus on physics and chemistry, consults on a few clinical research projects.

The Data Management Branch has created scores of computer programs for clinical scientists in the Institutes and for departments in the Clinical Center. Its Clinical Information Utility project provides the archival data base for information collected by the Clinical Center medical information system. DMB is working with members of the Institutes and Clinical Center to develop better systems to retrieve and analyze this archived data.

Finally, the Computer Center Branch provides the reliable, accessible, modern central computing facilities that support hundreds of clinical research projects and virtually all of the administrative activities without which research and patient care could not go forward at NIH.



Arnold W. Pratt, M.D.
DCRT Director

Contents

Computer Systems Laboratory 1

Provides consultation and collaboration in the design and implementation of specialized computer systems for laboratory and clinical applications.

Laboratory of Applied Studies 7

Relates mathematics, statistics, and computer science to such biomedical problems as ECG analysis, evaluation of physiological systems in health and disease, modeling of the microcirculation, and estimation problems in laboratory medicine.

Physical Sciences Laboratory 11

Conducts research in mathematical theory and practical instrumentation to explain biological phenomena in terms of chemistry and physics at subcellular molecular levels.

Laboratory of Statistical and Mathematical Methodology 15

Provides statistical and mathematical help in the computer analysis of biomedical data; offers statistical and mathematical packages for users; develops methodology in multivariate analysis, curve fitting, biological shape and pattern theory.

Data Management Branch 21

Serves as a central resource of systems analysis, design, and programming for data processing projects relating to scientific, technical, management, and administrative data.

Computer Center Branch 25

Designs, implements, and operates the NIH Computer Center; provides assistance, training, and technical communications to the more than 8,000 users of the Central Utility.

Office of ADP Policy Coordination 31

Coordinates the complex Federal policies and procedures that govern getting and using computers at NIH.

Office of Administrative Management 33

Provides general administrative management support for the Division's work.

Office of Scientific and Technical Communication 35

Serves as a central source of information about DCRT activities and about computer-related disciplines.



Computer Systems Laboratory

Alan M. Demmerle, Chief

Function and Scope of Work

The Computer Systems Laboratory--26 professionals representing the disciplines of engineering, computer science, medicine, and chemistry--is the major source of expertise at NIH for minicomputer and microcomputer technology. CSL engineers and scientists, in collaboration with NIH intramural laboratory and clinical investigators, apply this technology in the areas of laboratory automation and patient care. Some projects are occasionally undertaken with NIH extramural program staff and with other Federal agencies. CSL's multidisciplinary approach aids both the recognition of problem areas that will benefit from automation and the interpretation of research needs in terms of computer methods.

Computers may be used only in an adjunctive manner--for example, as a more convenient means to acquire laboratory and clinical data--or they may be integral parts of an elaborate instrumentation system, such as a computer-controlled mass spectrometer. Advances in large scale circuit integration (LSI)--the microprocessor revolution--have brought about the miniaturization of computer components and a dramatic decline in their prices and power requirements. CSL engineers are now able to use microprocessors to deal with problems that once defied solution because of cost, size, or manpower constraints.

CSL projects range in size from consulting activities of a few days' or weeks' duration to large-scale efforts taking many many years. Much CSL work involves the development of new methods or technology or is influenced strongly by the changing needs of research. Thus, it is often difficult to predict the long-term scope at the outset of a project.

FY82 Highlights

This year, CSL engineers and scientists worked on 32 projects, representing collaboration with almost

all of the NIH Institutes. Some of these projects require only limited resources, while others take many many years. The latter deserve particular emphasis because of both their sheer magnitude and the importance of the patient care or research activity they support.

One of these large scale efforts is the **Radiation Therapy Project**, a collaborative effort with the Radiation Oncology Branch, NCI. This project began in late 1975. Since then, it has experienced modifications to both the original goals and implementation techniques. At project inception, short-term priorities focused on integrating scans from a recently acquired CAT scanner into a computerized treatment planning system. More ambitious goals included three-dimensional treatment planning, treatment plan optimization, and dynamic treatment planning. Short-term goals were quickly achieved. Despite changes in program emphasis and significant technical problems, a limited three-dimensional capability has been implemented. Optimization requirements, however, have been reduced and are being satisfied through pseudo-optimization techniques that use interactive beam manipulation.

Aspirations for achieving dynamic therapy have remained dormant. Instead, efforts were expended upon supplementing traditional isodose curves with point dose calculations, upon producing implanted seed calculations, and upon generating sophisticated treatment plan displays that emphasize particular structures or magnify special features.

The original treatment planning system consisted of a Digital Equipment Corporation PDP-11/70 computer with treatment planning software developed by J. R. Cunningham and marketed by Atomic Energy of Canada Limited (AECL). Clinical use of this system began at NIH in 1977 in a single user mode. Two years ago, the AECL software was replaced by algorithms developed by J. Van de Geijn. Sophisticated displays featuring up to eight

beams, CAT or ultrasound scan, and point dose or isodose curves on one screen also have been operational for some time.

The core hardware configuration remains essentially the same as originally purchased except for the addition of new display equipment. However, the original single user software implementation has been replaced by new software that supports multiple treatment planning stations. The success of the system can be measured by its high use by the Radiation Oncology Branch, and by the fact that a number of commercial firms have expressed interest in including it in their product line.

Another major project in the Clinical Center that was completed this year is the computerized **ECG Management System**. The Heart Station of the Clinical Center is responsible for obtaining and interpreting electrocardiograms (ECG's) from hundreds of patients each week, and for maintaining a filing system for all previous ECG records.

With the impending completion and occupancy of the new Ambulatory Care and Research Facility (ACRF), the Clinical Center wanted a new comprehensive computer-based system to facilitate the processing of the projected ECG workload and to provide a practical method for long-term storage and retrieval.

The project's requirements included analog-to-digital conversions of ECG waveforms, computer-assisted interpretation of the ECG data, physician approval of all interpretations, automatic generation of final diagnostic reports, and generation and maintenance of a data base of all tracings and interpretations in machine readable form. An additional requirement was the ability to search the data base using selection factors to be specified by researchers engaged in the wide class of retrospective clinical studies envisioned for the ACRF.

CSL developed the Request for Proposals for the system in 1979. The procurement process culminated with the purchase of a Hewlett-Packard ECG Management System that was specifically configured and programmed to conform to the Clinical Center's operational procedures, reliability needs, and report format requirements. Relatively rapid installation of the computer system was achieved by using an existing computer site in Building 10. The Clinical Center's telephone network was adapted so that the system's portable ECG machines could be used to transmit ECG's from all patient care areas or patient rooms to the centrally located ECG computer facility.

Routine clinical use of the ECG diagnostic computer system began in January 1982 after a short

orientation session for the heart station's ECG technicians. CSL expects to provide software modifications to support future research protocols.

Other major clinical activities on which CSL worked during FY82 are as follows:

- **Intensive Care Units (ICU's):** CSL is involved in the automation of three ICU's. The general goals are to capture patient vital signs, generate comprehensive displays of patient status and trends on demand, and substantially simplify medical recordkeeping. Data archival is expected to facilitate research in areas such as noninvasive intervention.
- **Nuclear Medicine:** In this project, the design and implementation of a stand-alone computer system facilitates the analysis of digitized patient brain scans obtained on floppy discs from the Nuclear Medicine Department's PET Scanner. Three Institutes currently use this system for diagnostic purposes and for pursuing basic research in the areas of schizophrenia, epilepsy, and aging.
- **Gait Laboratory:** The Automated Biomechanics Laboratory System involves the measurement of limb and spine position in space, forces in the hand and between foot and ground, and electrical activity of limb muscles. Designed for use with arthritic, orthopedic, and neurological patients, as well as amputees, it is anticipated that the data collected will assist in the evaluation of drug therapy and orthotic and prosthetic devices.
- **Clinical Pathology:** Work with the Clinical Center's Clinical Pathology Department centers on the automation of laboratory procedures that have resisted computerization by conventional methods. A major innovation is the development of a microcomputer-based system to facilitate the recording of differential white cell counts.
- **Pulmonary Laboratory:** Automated methods for evaluating pulmonary function using such procedures as measurement of pulmonary compliance and work of breathing and exercise testing on a treadmill have been developed. The goals are improved speed and accuracy in test performance and evaluation by the NHLBI staff who provide this service in the Clinical Center.

In the laboratory automation area, CSL work on the **Distributed Laboratory Data Acquisition and Control System (DLACS)** for the laboratories of NIADDK in Building 2 was largely completed this year. Planning and design of this system began in 1976; it replaces a centralized data acquisition and processing system developed by CSL over a decade

ago. The system is designed as a local computer network consisting of a group of microcomputers that communicate with a host processor by way of a front-end communications processor that, in turn, performs a file store-and-forward function. Each satellite microcomputer performs data acquisition and control for a single instrument or experiment. Acquired data files may be stored locally, however, they are normally transferred via the network to the host processor.

Development of DLDACS was phased over a period of several years to avoid interfering with the research of users of the old, centralized data acquisition system. In fact, the communications processor initially was connected to the old Honeywell-516 central computer, and one satellite microcomputer was put into operation early in 1979. Since then, additional satellites have been added, one at a time, in place of the hardwired instrument interfaces used in the old system. There are currently eight satellite processors in use. This year, the final step of replacing the H-516 processor with a multiuser DEC PDP-11/70 was made. Because of the design of the local network, this major accomplishment was completed without requiring any changes to the satellite microcomputer software.

Other large CSL projects in NIH Research laboratories during FY82 were:

- **Electron Microanalysis:** CSL is collaborating with the Biomedical Engineering and Instrumentation Branch, DRS, in the development of an automated electron microanalysis facility for use by NIH scientists. It will be used for research into the elemental composition of biological specimens and for developing new techniques in electron microscopy. Some of these, such as electron energy loss imaging, can only be done with the aid of a computer.
- **FMF Cell Sorters:** CSL pioneered data management systems for FMF cell sorters at NIH. Support for data acquisition, display, and analysis is provided for four Becton-Dickinson FACS II FMF/Cell Sorters. Two additional FMF/Cell Sorters used at the Naval Medical Center in collaborative programs with NCI are also supported.
- **Molecular Interactions System:** A microcomputer-based data system supervises the acquisition and processing of information from an analytical ultracentrifuge and a circular dichroic spectropolarimeter used in NHLBI to investigate the interactions between human lipoprotein subunits. Capabilities include acquisition, display, and preprocessing of data

from the ultracentrifuge and spectropolarimeter. After limited local processing, files are transferred to the central facilities' PDP-10 for further processing.

- **Animal Management:** The Small Animal Section of DRS supplies large numbers of rodents to NIH investigators and also serves as an international genetic resource. CSL is assisting the Section in the design and procurement of a computer system to improve their colony management and breeding research programs. CSL also invested considerable effort this year in the development of new computer-related technology to support biomedical and clinical research.

The **Medical Information Technology Project**, now in its third year, achieved a major milestone this year with the installation of a computer in a physician's office for field trials. This project involves research into source data automation techniques for patient-physician encounters in primary care settings.

One outgrowth of the project is a system that (under the physician's supervision) automatically produces prescriptions and advice on followup home care, both of which are keyed to diagnosis. It is this prescription and advice system, initially tailored for use in a dermatologic practice, that is undergoing field trials.

In operation, the physician gives the system a diagnosis for the patient examined, followed by the selection of one or more drugs appropriate for that diagnosis. The system's drug formulary contains medications the physician would normally prescribe. Using this formulary, the system displays a default formulation for each drug prescribed based on the diagnosis and, when necessary, on other factors such as the patient's age, sex, or weight. The physician may simply approve the default selections or he may alter them to fit particular circumstances. Once approved, the computer prints the prescriptions on blank prescription forms.

In addition to the drug formulary, the computer system's data base also contains numerous generic advice 'modules' containing advice on followup home care, additional information about a drug and its use, and disease information. Based on the diagnosis and the medication regimen prescribed, the computer, again subject to the physician's supervision, selects from among these advice 'modules' and tailors them to the situation at hand. As is the case with prescriptions, the computer then prints them for the patient.

The computer system just described benefits both the physician and the patient. The physician's time is

saved because the computer produces accurate, legible prescriptions, thus eliminating the need to write them in longhand. Furthermore, summaries of the prescriptions and instructions to the patient can be produced for inclusion in the patient's record. The patient benefits by receiving detailed printed instructions about his disorder and any drugs prescribed for him. Thus, problems resulting from the patient forgetting or misunderstanding instructions given to him orally by the doctor may be avoided.

The **Image Processing System**, another area of advanced technology, involves the implementation of both general-purpose and special-purpose hardware and software to meet the growing image processing requirements of the NIH community. Until recently, this effort was conducted using the Evans and Sutherland facility at DCRT, however, a new system using state-of-the-art equipment has been designed and is being procured. It is expected that a special application of this technology will be to provide the NIH Clinical Center with a medical imaging network.

Future Plans/Trends

FY83 can be expected to present an increased demand for computers in laboratory and patient care settings. More complex research goals of biomedical research investigators point to a greater need for automation in the laboratory. Technological developments in large-scale circuit integration continue to lead to lower costs and smaller sizes for computers. The current popularity of 'personal' computers is resulting in greater awareness on the part of NIH scientists of the potential benefits of computers. Concurrently, in common with many other organizations, CSL is faced with contracting personnel and budgetary resources.

In response to the challenge imposed by this conflicting set of circumstances, CSL expects to maintain high quality engineering and laboratory computer support to NIH programs by continuing policies developed in the past for managing resource issues. For example, CSL staff will continue to be deployed on projects promising maximum impact to the NIH community--those that serve a significant number of scientists, affect the quality of patient care, or represent general-purpose developments.

Finally, a trend toward greater emphasis on software engineering, begun several years ago with the introduction of microprocessors, is expected to continue with concomitant improvements in productivity. Many of CSL's engineering design functions--instrument interfaces, data acquisition devices, special signal processors--are now accomplished with microcomputers. Because of the adaptability of software, these new design concepts readily meet the changing needs of research programs.

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Laboratory of Applied Studies

Eugene K. Harris, Chief

Functions

The Laboratory of Applied Studies (LAS) has three main purposes:

1. in collaboration with biomedical scientists, to apply mathematical theory and computing science to the construction, testing, and improvement of mathematical models of physiological processes--particularly reaction-diffusion kinetics, transport of substrate to tissues, and the control of metabolism within cells and tissues;

2. in collaboration with clinicians, to develop and apply mathematical or statistical theory and special-purpose computing procedures (analog or digital as required) to facilitate research projects aimed at improving the diagnosis of disease and assessment of treatment;

3. to engage in independent research in applied mathematics, statistics, and computer systems necessary to provide a sound theoretical basis for collaborative studies, and to insure that state-of-the-art mathematical and computational methods are available as research tools at NIH.

Two sections carry out these primary LAS functions:

Applied Mathematics Section--AMS--(John E. Fletcher, Ph.D., Chief). This staff of five includes specialists in applied mathematics, computer science, biomathematics, and medicine.

Medical Applications Section--MAS--(James J. Bailey, M.D., Chief). This five-member staff includes physician-scientists, electronic engineers, and computer systems analysts.

The Chief, LAS, is a biostatistician with training in public health and the basic medical sciences.

Scope of Work

The Laboratory of Applied Studies works on projects in basic and clinical biomedical science. Largely, these involve collaboration with other groups at NIH, elsewhere in the U.S.A., and abroad. The collaborating investigators this year included:

- *biochemists and pharmacologists* at NIH, at the Medical College of Virginia, and at other universities in the U.S.A. and in France working on models for receptors of drugs or other ligands, on the kinetics of enzymes in membranes, and on other problems in tissue metabolism
- *physiologists and chemical engineers* in the U.S.A and Europe studying the transport of substrate within the microcirculation and the regulation of tissue perfusion
- *clinicians* in the cardiology, pulmonary, and hematology branches of NHLBI; in the arthritis and rheumatism branch of NIADDK; and in the medical intensive care unit and the departments of diagnostic radiology and diagnostic imaging of the Clinical Center
- *clinical chemists and pathologists* at NIH (Clinical Pathology Department, Clinical Center) and elsewhere in the U.S.A., in Europe, and in Japan engaged in the collection and study of reference values in laboratory medicine
- *electrocardiologists and biomedical engineers* in the U.S.A., Canada, and Europe concerned with improved algorithms for computer-based interpretation of ECG's and evaluation of ECG interpretative programs.

Highlights of the Year's Activities

Work continued in computer-based studies of pulmonary gas exchange during exercise in patients with respiratory disease. Despite unfortunate delays due to problems with the vendor-supplied software, which have now been resolved, considerable progress can be reported in this collaborative project with the Pulmonary Branch and the Clinical Hematology Branch, NHLBI. Interfaces to the exercise equipment to enable online computer control have been designed and built by Drs. R. Burgess and E. Pottala, while system programming for realtime control of these devices and for analysis

of accompanying data on CO₂ and O₂ pressures and content is being completed by M. Horton. Preliminary studies of healthy subjects have begun.

Dr. A. Albert, Fogarty International Research Fellow in LAS, has contributed to the theory of dynamic risk assessment in acute disease by creating very general, yet practical, methods for sequential analysis of time-dependent multivariate measurement vectors obtained during the course of the patient's illness. Combining these methods with discriminant function techniques enables daily reassessment of probable patient outcome. The procedures have been applied successfully to patients under intensive care following myocardial infarction. In addition, Dr. Albert has published a generalized theory and method of computing multivariate likelihood ratios for combinations of discrete and continuous variables. This work represents a substantial advance in the calculation of diagnostic probabilities (predictive values of specified illnesses).

Theoretical work by Dr. M. Bieterman on the adaptive finite element method for the solution of reaction-diffusion equations resulted in new software routines for the efficient cost-effective solution of many of the complex systems of partial differential equations that arise from biological models. These routines, known as Femol1 are now available on the NIH central computer systems.

Studies by B. Bunow and E. Pottala of network modeling languages have demonstrated that network models are feasible for use as biological simulators. Although computer times for these models on the NIH central system are presently excessive, their use on dedicated systems such as the VAX or similar machines has established their utility. Presently, interested NIH scientists are being instructed in network methods, and exploratory applications are underway in collaboration with NIH researchers on problems of nerve conduction and facilitated diffusion in tissues. One advantage of these simulations is that a functional rather than a mathematical description of the biological process suffices as a requirement to initiate study of its stimulus-response characteristics.

A comprehensive report summarizing Dr. J. Fletcher's past decade of research on the analysis and interpretation of equilibrium binding data through mathematical models has been completed and is being distributed to interested scientists worldwide.

During FY82 LAS staff members participated in various teaching and consulting, or advisory, activities.

J. Fletcher continued to serve as Chairman of the Mathematics and Computer Science Departments, Foundation for Advanced Education in the Sciences.

J. Bailey continued as a member of an NHLBI visiting team concerned with computer analysis of exercise ECG's. He also serves as consultant on common standards for quantitative electrocardiography for a program in medicine and public health, sponsored by the European Economic Community.

E. Harris continued to be a consultant in applied statistics to the Food and Drug Administration's Division of Medical Devices and Diagnostic Products. Dr. Harris also serves as consultant statistician to the College of American Pathologists and to the International Federation of Clinical Chemistry (Expert Panel on the Theory of Reference Values), and is a member of the Board of Editors of *Clinical Chemistry*.

Future Plans

Testing of the computer-controlled system for measuring pulmonary gas exchange in exercise will continue on healthy volunteer subjects. Studies to evaluate cardiorespiratory abilities in patients and controls will be specified in cooperation with the Pulmonary and Clinical Hematology Branches of NHLBI. A new project in cooperation with the Department of Critical Care Medicine, CC, to investigate dysfunction in neurologically impaired patients will be pursued through development of microcomputer-based methods for analysis and display of evoked potentials.

Utilizing the newly upgraded DeAnza image processing system, a joint study with the clinical neuropharmacology laboratory, NIMH, will continue to develop theory and methods for interpreting electron energy loss spectra from ultracellular biological specimens, particularly in the study of dense bodies in electron micrographs of blood platelets.

The analysis of the signal/noise characteristics of various parameters of regional ventricular wall motion will continue jointly with the Nuclear Medicine Department, CC, and the Cardiology Branch, NHLBI, in an effort to improve differential diagnosis of coronary artery disease and other cardiac myopathies.

A major effort will be made to facilitate the conversion of network models simulating biological processes into forms compatible with languages such as MLAB to enable the use of powerful data-

fitting algorithms. Training of and collaboration with NIH scientists using network simulation modeling will continue. In the area of numerical analysis, the current program for approximate solution of partial differential equations (FEMOL1) will be extended to sets of 3 or more equations, enabling it to be of more general use to NIH scientists using biomathematical models.

Statistical theory developed to support the calculation of reference values for the differences between two or three successive measurements of blood constituents will be published and its application extended through collaborative studies of selected patient groups. Investigation of relative sensitivities of multivariate and univariate reference ranges will progress using clinical chemistry data and followup diagnostic information from a large health maintenance program.

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George H. Weiss, Chief

Function and Scope of Work

The Physical Sciences Laboratory carries out research in support of NIH programs and in pursuit of its members' interests in the areas of physics, physical chemistry, applied mathematics, and applied computer technology. It has an active research program in its areas of expertise and provides consulting services to other NIH scientists in theoretical physics, chemistry, and applied mathematics. Members of PSL develop theory and often develop instrumentation for biomedical experiments.

The PSL staff consists of seven professionals who work in the areas of:

- biophysics
- light scattering, as applied to problems in determining structure and function of biologically interesting gels and other forms of matter
- nuclear magnetic resonance, as applied to kinetic and configurational properties of molecules
- the use of image processing techniques to interpret electronmicrographs of membrane structure
- the physical chemistry of actin, and
- applied mathematics in areas suggested by investigations at NIH.

All of the members of the Laboratory collaborate with scientists both on and off the NIH campus. For example, crystallographic data bearing on intermolecular forces is generated at Brock University, Canada, in collaboration with members of PSL in a joint theoretical and experimental project in that general area. A new project has been initiated together with members of the Clinical Center and the Computer Systems Laboratory, DCRT, on the use and interpretation of ultrasonic data in the study of tongue motion in different parts of speech.

FY82 Accomplishments

A joint project between members of PSL and Brock University has succeeded, for the first time, in directly measuring the force between biological macromolecules. This has provided a good picture of how the force between parallel DNA helices behaves in response to changes in distance, as well as elucidating the effect of structure on this force. An extension of this work will allow the determination of important thermodynamic parameters of proteins.

The applicability of two-dimensional Fourier Transform Spectroscopy to the determination of kinetic parameters for enzyme reactions was demonstrated for the first time, in a study of the isomerization of glucose-6-phosphate. This work required not only the techniques of physical chemistry, but also the development of a suitable theory as well as the study of the effects of instrumental noise on the calculation of parameters.

Work has continued on light scattering techniques as applied to the determination of mechanical rigidity and internal viscosity of polymer gels. The current emphasis is on the structure and properties of polyacrylamide gels because of their technological importance, but studies are also underway on gels formed from glycoproteins and clots formed from reconstituted human plasma. This research requires expertise both in the development of a considerable body of theory to interpret experimental data as well as experimental skill in the modification of available equipment to perform the relevant measurements.

A theory of errors of parameter estimates in positron emission tomography has been developed and will be incorporated into programs in use on the PET scanner. This theory is part of a continuing study of the optimal design of experiments that includes present analyses of NMR and chromatography experiments in addition to the PET study.

Dr. Adrian Parsegian has been elected President of the Biophysical Society. Dr. George Weiss has been appointed Biostatistics Editor of *Cancer Investigations*.

PSL partially sponsored an international meeting on Random Walks in Physics and Biology, which was held at the National Bureau of Standards from June 28 to July 1, 1982. Dr. George Weiss was Chairman of the organizing committee for the meeting.

Future Plans/Trends

Research in PSL will continue along lines already initiated. A new joint project with the Speech Pathology Department of the Clinical Center and CSL will study the combination of ultrasound and image processing techniques on the study of tongue position in speech.

With the recent access to an x-ray spectrometer on the NIH campus, Drs. Parsegian and Lee will be able to extend their measurements of intermolecular force constants to study nucleic acids. A large project is being planned on the use of molecular graphics programs to investigate molecular contacts in protein crystals.

Further studies will be undertaken in the relation of instrumental noise to the precision of parameter estimates in NMR measurements. These studies should point the way to optimization of such experiments. Dr. Ferretti will be joining NHLBI in the near future but collaboration on these problems will continue.

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Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

Function and Scope of Work

The Laboratory of Statistical and Mathematical Methodology (LSM) combines research in mathematical statistics, mathematics, computer, and information science with collaboration and service in these areas to NIH researchers and administrators. LSM staff interact with all NIH Institutes, with other Federal agencies outside DHHS, and with biomedical researchers worldwide.

In addition to the position of chief, the Laboratory has fourteen full-time professional positions distributed among four sections:

- The **Statistical Software Section (SSS)** provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis, including selection and support of large systems/packages. Three specialists in scientific programming are led by a computer systems analyst whose specialty is statistics.
- The **Biomathematics and Computer Science Section (BCS)**, directed by a mathematician, performs independent research and provides consultation and collaboration in the specialties of its four computer and mathematical scientists.
- The **Statistical Methodology Section (SMS)** works closely with the Statistical Software Section. Two professionals in mathematical statistics provide biostatistical consultation and do independent research.
- The **Medical Information Science Section (MIS)** investigates and develops methods for application of information and computer science to medical language data processing. Two computer specialists work under the direction of a computer systems analyst who is an expert in computational linguistics.

A major part of LSM activity is the offering of statistical and mathematical systems/packages to the NIH user community. LSM accepts responsibility

for evaluation of new systems/packages and their suitability for NIH. When it offers a system/package to the NIH community, LSM makes three basic commitments:

1. Maintenance of the package, with adequate documentation, through NIH computer system changes, system/package updates, and corrections.
2. Rapid response to queries concerning user access to a system/package program, including job control language and program parameters.
3. Assistance in interpretation of results.

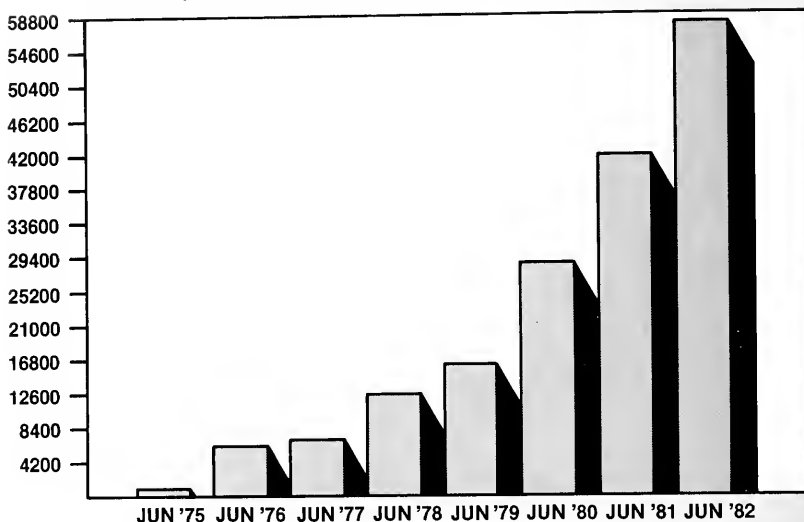
During this year, as in the past year, the Statistical Software Section of LSM maintained the following systems/packages and programs on the IBM 370 system of the DCRT Computer Center:

- BMD and BMDP, Biomedical Computer Programs, UCLA.
- SPSS and SCSS, Statistical Package for the Social Sciences, SPSS, Inc.
- SAS, SAS/GRAPH and SAS/ETS, Statistical Analysis System, SAS Institute, Inc.
- P-STAT Statistical Package, P-STAT, Inc.
- IMSL, International Mathematical and Statistical Libraries, IMSL, Inc.
- MSTAT1, Collection of Mathematical and Statistical Programs, DCRT.

In FY82 alone the SSS staff responded to over 5,500 queries concerning use of these packages. Also during this year, every system/package went through at least one major update.

The Biomathematics and Computer Science Section maintains several systems/packages and specialized systems on the DECsystem-10 of the Computer Center. Foremost in use is the interpretive system MLAB, designed (by LSM scientists) for biomathematical modeling. C-LAB, previously an independent package for pattern recognition and cluster analysis, has now been incorporated into MLAB. The Unified Generator Package, written and maintained by a BCS staff member, is on DCRT's IBM System 370.

Uses per month of
Statistical packages supported by LSM*



*Packages supported by the Statistical Software Section only. Does not include packages supported by the Biomathematics and Computer Sciences Section.

As a result of LSM's policy of not only supporting the use of these systems/packages but also aiding in the interpretation of their output, the statisticians of the Statistical Methodology Section provide consultation over a wide range of scientific fields. Some very brief consultations are very successful because there is a known answer to the question at hand. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

Research projects in LSM vary widely, from studies of natural language processing for medical information systems and studies of efficient algorithms for information retrieval to studies in mathematics and statistical methodologies for biomedical applications.

FY82 Accomplishments

FY82 was LSM's eighth year as a separate entity within DCRT. The volume of its computational and consultative services continued to expand; its research activities decreased slightly, with one project terminated.

Computation

In FY82, LSM continued to expand teaching and documentation for supported systems/packages. LSM taught eight introductory courses for SAS, two for SPSS, and two for BMDP. In addition, two introductory courses and one advanced course were taught for MLAB, plus an introductory course for BRIGHT (a package supported by DMB) and two courses on computer graphics at NIH. The tenth edition of the *MLAB Reference Manual* is now being printed. The *DCRT Mathematical and Statistical Program Manual* was updated in FY82.

BCS staff contributed to the implementation of overlay facilities on the DECsystem-10, and MLAB was redesigned in a segmented form to use overlay, so that software for seldom-used operations is loaded into computer memory only when needed. MLAB software was substantially enlarged by incorporation of C-LAB operators, of new OMNIGRAPH character fonts and codes for display of mathematical formulas, and of new, more informative error messages.

Consultation, Collaboration, and Research

As in FY81, LSM consultation and research in FY82 was closely tied to the use of the computer. Most consultations (55 percent) involved statistical advice combined with considerable computer use. Others (40 percent) involved computer use alone and a small fraction (5 percent) involved mathematical or statistical advice with only limited computer use.

In FY82, LSM research, collaborative, and consultative efforts merged more closely and were less distinguishable among themselves. In a number of studies, statistical methodologies were developed for, or modified to suit, specific biomedical problems.

The results of LSM research on simultaneous confidence intervals for ratios appeared in the *Journal of the American Statistical Association* in 1982. A study was completed on the connection between statistical and algebraic independence, applicable to the sample covariance matrix of multivariate data.

In statistical discriminant analyses--a subject of LSM research in collaboration with Dr. J. Darroch, Flinders University, South Australia, and Dr. H. Hoffman, DRS--methods adapted for size and shape variables

are being used to study genetic variation in laboratory mice with reference to purity of breeding stocks. A separate study of independence of size and shape variables before and after scale change appeared in FY82, along with other LSM studies of statistical distributions. A collaborative study was undertaken with Dr. P. Turkeltaub (BB/DPB) on clinical symptoms and allergic reactions to pollen. LSM also participated actively in a study of Chagas disease (Dr. F. Neva, NIAID/LPD) and continued collaborative work in various studies of schistosomiasis (Dr. A. Cheever, NIAID/LPD).

New studies in linear models were initiated in FY82, and two of these have been completed. The first gives optimal linear model estimates of variance components, while the second presents a solution to the multivariate analysis of variance with unbalanced data. A collaborative study on the spatial distribution of blue cones in the retina with Drs. S. Schein (NEI/CB) and F. de Monasterio (NEI/LVR) is near completion. An algorithm related to this work has been published. A study of patients with systemic lupus erythematosus in collaboration with Dr. T. Chused (NIAID/LMI) is near completion.

In computer science, a study of hashing with coalescing lists for information storage and retrieval was completed and submitted for publication. A method of resolving overlapping spots on two-dimensional electrophoretic gels was studied; programs implementing the method are under development. Studies of equivalence of module theories and of classification of Riemannian geometries by N-algebras (with possible applications to size and shape analysis) continued. A pilot study of computer 'reading' of technical text was completed. This involved computer translation of syntactic and semantic content of a simplified chapter of a computer programming textbook into operational structures in the procedural language PROLOG.

In medical linguistics, research studies on the morphosemantic structuring of medical terms derived from Greek and Latin were continued. Previous work on computer parsing of medical words into morphemes via suffix analysis was extended to more than 1,500 terms representing 6 kinds of surgical procedure. The results are applicable to the construction of dictionaries suitable for information retrieval by computer. Also studied were rules for morphosemantic transforms useful for computer substitution of terms in the automatic encoding of medical text. The MIS-developed encoder program for automatic assignment of SNOP (Systematic

Nomenclature of Pathology) codes to surgical pathology diagnoses was used on a routine basis (Dr. J. Costa, NCI/LP). Collaborative studies on the improvement and modification of the SNOP dictionary with Dr. Donald E. Henson (NCI/BCPC) continued in FY82. An LSM linguist also served as a consultant on a machine translation project at Georgetown University.

LSM research on the 'symmetric axis' method of describing biological shapes was discontinued this year, due to the retirement of the principal investigator. Computer software for symmetric axis analysis and reconstruction of figures will be maintained. Programs and documentation are sent to biomedical researchers on request.

Future Plans/Trends

No major shift in laboratory service or research is anticipated in the coming year. Current levels of statistical and mathematical systems/packages support, consultation, and user assistance will be maintained. Research projects will be continuations of those already initiated and reported here.

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Data Management Branch

J. Emmett Ward, Chief

Functions and Scope of Work

The Data Management Branch (DMB) provides advice and assistance to research investigators, program officials, and administrators throughout NIH in planning for and obtaining computer data processing services. In this role the branch is a central NIH resource for systems analysis, design, and programming. There are currently 47 permanent full time employees whose disciplines include computer science, mathematics, and statistics.

DMB staff design and create computer-based data management systems that provide practical solutions to the unique mix of administrative, scientific, and management data processing problems encountered at NIH. Each new computer system user is provided comprehensive training in all system facilities and functions of the system provided by DMB. In addition DMB staff teach courses about programming tools; provide advice on data management techniques to NIH programmers; serve as consultants to the B/I/D's for obtaining and monitoring contracting services for computer systems development; and create and maintain general purpose, user-oriented programming tools to speed building and improve operation of applications systems.

DMB comprises five sections. The **Applied Systems Programming Section (ASPS)** and the **Scientific Applications Section (SAS)** provide general computer systems analysis and programming services for all of the B/I/D's. The ASPS supports general data management, and the SAS handles those projects that require scientific data analysis.

The **Data Base Applications Section** and the **Data Base Enhancement and Control Section** develop and maintain the central administrative data base for NIH materiel and financial management. The **Clinical Support Section** develops and maintains the Clinical Information Utility as a data base for research and patient care in the Clinical Center.

FY82 Accomplishments

The Clinical Information Utility is a long term effort that, when completed, will provide a unique archive of integrated data for use in patient care and research. Efforts to date have involved the development of software to acquire and to make available data from the Medical Information System and the individual clinical service activities. The integration of these individual data bases has now begun. The design of this effort will provide users with a single source for most of the clinical service data and all of the medical information system data. It will allow authorized users to make requests for information and will provide either reports or sub-files of the data, which will be produced in a format acceptable to BRIGHT for further perusal and analysis.

BRIGHT is a user-friendly interactive program designed to make data entry, correction, updating, manipulation, retrieval, formatting, and printing of tabular data bases easier. The first DCRT training course for BRIGHT was taught in early December 1981 and a formal seminar introducing the system to the clinical associates was conducted in March 1982 in the Clinical Center. BRIGHT has had several new features added during the fiscal year and it is a much more versatile and easily used package for data and graphics display, table-making, computation, and analysis.

To assist the Records Processing Section in the Medical Records Department of the Clinical Center, a tracking system for the medical records audit process was designed and implemented. This system provides a mechanism for monitoring the status of medical records in process and for following up with physicians concerning delinquent reports. This system has had a significant impact in that it has not only reduced the manual effort involved in the audit process but also improved the organization of the followup procedure.

The NIH Administrative Data Base is an ongoing development project that uses data base technology in support of NIH-wide materiel and financial management. This project expanded on several fronts. A vendor credit system was added to the accounts payable procedure; an alphabetic search capability was made available for the vendor data base; all miscellaneous obligations such as training orders, utilities, tuition, work requests, etc., were programmed to flow through the ADB; and a facility to produce Purchase Orders (SF-147's) online was added for reprints and professional services.

Extending the availability of ADB functions to the B/I/D's is also well under way. In collaboration with the Office of Research Services and the Training Assistance Branch, DPM, B/I/D terminal locations have been identified and contracts have been negotiated for conducting training on delegated procurement and receiving. Current plans call for all B/I/D's to be making full use of these functions by early Fall, 1982.

From July 1982 through February 1983 the stock requisitioning and the central and self service stores' inventory systems will be phased in. Full conversion to this new set of functions should be in place by the end of the first quarter of calendar year 1983.

Development of the new financial management system for the ADB is under way and a detailed design document should be available in November 1982. Plans call for implementing the fund certification, fund control, and general ledger modules of this system by utilizing off-the-shelf software, modified to fit NIH requirements.

For a detailed review of the many other important projects in which the Data Management Branch has been involved, please refer to the project reports in Volume 2. These projects are too numerous to highlight in the summary.

In the area of general support for NIH activities, DMB continued to maintain and teach courses on the Inquiry and Reporting System (IRS) and MARKIV; to support NIH use of Chemical Biological Activities (CBAC) and Biosciences Information System (BIOSIS) current awareness searches on a biweekly and semimonthly basis, respectively; to maintain and distribute the NCI Survival System; and to consult with and assist NIH programmers and contractors, enabling facile use of DCRT computer facilities.

Future Plans/Trends

During the next year, the Administrative Data Base will expand to include all central inventory functions and work will have begun to bring other inventory systems (e.g., Planning and Control Branch, Biomedical Engineering and Instrumentation Branch, and Pharmacy) under this umbrella. The financial management system fund certification, fund control, and general ledger modules should be well on their way to completion by the end of FY83. Stock requisitioning should be installed in all of the B/I/D's and open market requisitioning should be ready for a pilot test by the end of the next fiscal year.

The Clinical Information Utility will have a completely integrated data base that will provide an effective link among the user, the clinical data and the analysis.

Its role as a central resource for computer applications development throughout the B/I/D's will continue to receive primary support by DMB.

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Computer Center Branch

Joseph D. Naughton, Chief

Function

The Computer Center Branch (CCB), the largest component of DCRT, designs and operates the NIH Central Computer Utility and its associated telecommunications facilities; conducts a formal computer training program; and provides technical documentation, programming support, and consultation on the use of computers in support of scientific and administrative programs throughout NIH.

Because the Computer Center receives no direct appropriation, all services are provided strictly on a fee-for-service/cost recovery basis.

Two large, interconnected, multicomputer facilities--the IBM System 370 and the DECsystem-10--form the nucleus of the NIH Computer Utility. Each facility is linked by telephone lines to hundreds of remote interactive terminals and computers located throughout NIH and many other Federal agencies. System software is either designed and implemented by Computer Center personnel or acquired from other sources and adapted to meet the unique needs of the NIH biomedical research and administrative user community.

A specialized staff of professional, technical, and administrative personnel keep the NIH Computer Utility functioning smoothly 24 hours a day. Experienced computer systems programmers and analysts develop and maintain operating system software. They also offer technical consultation, design and teach training courses, and write technical documentation on the use of the Utility. A staff of experienced computer systems technicians operates the Computer Utility's hardware and telecommunications network, and provides data entry services. Systems management professionals establish long term program goals and ensure the design integrity of the Utility.

A number of research and development projects are also conducted by the Computer Center. These

include the design and installation of data security facilities for over 300,000 online data sets, the design and implementation of communications networking facilities to make possible the rapid exchange of information among research investigators, the development of improved graphic output facilities, and the exploration of new training methods.

Scope of Work

The NIH Computer Center plans, designs, implements, and operates a large, general-purpose Central Computer Utility. This Utility provides a variety of computational services in support of a dynamic and diverse user community of over 10,000 research scientists, administrators, secretaries, and programmers throughout the Federal Government.

The primary component of the NIH Computer Utility is a uniquely configured, 'loosely coupled' system designed around 5 IBM 3081 processors with 80 million bytes of directly addressable memory. A peripheral complex of 115 tape drives, 300 disk drives, 2 mass storage systems, 11 high speed printers, card reader/punches, microfiche output units, and teleprocessing facilities for over 1,000 communications lines assure adequate data storage, input/output, and communication capabilities. Over 2,000 interactive terminals and 143 Remote Job Entry (RJE) computers located in users' offices and laboratories make the power of the Utility available at the source of the problem whenever needed.

Operating in a multiprogramming mode, this facility provides timesharing and batch processing, graphic services, and data base management facilities. The IBM System 370 facility operates 24 hours a day, and it currently processes over 13,000 batch jobs and 7,000 interactive sessions daily.

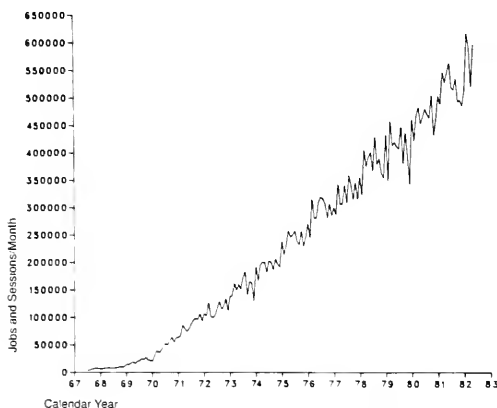
The other major component of the NIH Computer Utility is the DECsystem-10 timesharing facility. This facility is designed around one DK and two KL-10

processors with five million bytes of directly addressable memory, and it provides timesharing services and data communications support to over 2,000 laboratory research investigators throughout NIH. Ten tape drives, 31 disk drives, and a variety of teleprocessing facilities make up the peripheral complex.

The NIH Computer Utility provides a variety of programming languages—including FORTRAN, COBOL, PASCAL, BASIC, Assembler, PL/I, and SAIL—as well as a data base/data management system (IMS), the TELL-A-GRAF interactive graphics package, and a comprehensive library of statistical and utility programs. Online computing and batch job submission are available interactively on the IBM System 370 through WYLBUR and TSO, and through timesharing services on the DECsystem-10. Several facilities for job output on paper and microfiche are available, and there are programs for creating two-dimensional or three-dimensional graphic displays for advanced research projects.

The users of the Computer Utility's IBM System 370 are informed of current programming standards and available facilities in a comprehensive manual, the *Computer Center Users Guide*. The *DECsystem-10 Timesharing Guide* provides similar information for users of this system. Changes in the Utility are announced to users through *INTERFACE*, a periodic technical newsletter. An in-house training program offers 40 courses four times a year, to help users develop expertise in the use of the Utility.

NIH COMPUTER UTILITY System 370 Services



Through the years, the workload of the NIH Computer Utility has increased steadily.

Highlights of FY82 Accomplishments

As in past years, the user demand and workload of the NIH Computer Utility showed steady growth in 1982. A record number of jobs—over 6.5 million—were processed on the IBM System 370 during the year, and over 93 percent of these jobs were completed and available to the user in less than two hours. The DECsystem-10 facility also ran at a record pace, processing approximately 120,000 interactive timesharing sessions during the year. Overall, the Computer Utility processed an average of 26,000 job-sessions per day, a seven percent increase over last year.

A major highlight of the past year was the completion of an eight-month transition plan for installing the newly acquired IBM System 370 hardware. Over 100 hundred new tape drives, 250 disk drives, and 5 new Central Processing Units were put into productive use without interrupting normal service. The new IBM hardware has increased power, capacity, and reliability to meet the growing needs of Computer Utility users. Major new IBM System 370 components installed during the year include:

- Five 3081 Dyadic Processor Complexes—IBM's most powerful processor, the 3081, supports two processors in one physical unit. Each 3081 processor provides more than twice the processing power of its predecessor, the 3033 processor, in a unit smaller than a single 3033. Installation of the 3081 complexes resulted in a dramatic improvement in batch job turnaround time and interactive response time, and has increased the capability for processing complex applications in the most cost effective and efficient manner possible.
- One hundred fifteen 3420-6 drives—These advanced tape drives increase the speed and reliability of tape processing through the use of 6250 bpi reading and recording density.
- The 3380 Direct Access Storage Device—The 3380, IBM's newest disk drive, can store three times as much data as the 3330 disk it replaces. The 3380 also has a data transfer rate that is twice the speed of the older 3330 units. Online data storage was restructured to permit storage of data sets that range in size from a few bytes up to many millions of bytes. Over 300,000 online user data sets were successfully transferred to the new 3380 disks. The increased availability of high speed online storage, a direct result of the conversion to 3380 disks, made it possible to phase out the technologically obsolete 3330 private mountable volumes. Use of 3380 disks for online data

storage substantially improves the capacity and cost-effectiveness of the NIH Computer Utility.

- IBM 3850 Mass Storage System (MSS)--The MSS became fully operational this year, resulting in a significant improvement in turnaround time. This also increased cost effectiveness, expanded online storage capability, and permitted substantial amounts of offline data to be stored online inexpensively. Data space equivalent to more than 29 billion bytes has already been allocated on MSS volumes (at about one-ninth the cost of online direct access data storage space). Implementation of the 3850 MSS has allowed the maximum size of online data sets for batch jobs to be quadrupled. Users have found that the low charge for MSS storage, in addition to the savings that arise from fewer tape and disk mounts and faster processing time, make the MSS a very attractive alternative to other data storage media. The 3850 MSS has also been made available, through the MERCURY intersystem file mover, to users of the DECsystem-10 for storage of large rarely-accessed files.

The installation of the new processors and storage devices expanded the computational capability of the NIH Computer Utility dramatically. As a result, the limits on CPU time, scratch disk space, region size, and terminal idle time were all increased. This permits user batch jobs and interactive sessions to use significantly more of each of these resources. In addition, a new job class (class E) was established to serve the needs of the larger job that does not require volume mounting. The new larger limits improve job turnaround time, permit greater flexibility in job class selection, and allow the running of larger jobs during the prime shift.

DECsystem-10 users also received significant enhancements in timesharing services during the year. The installation of the latest version of the Symmetric Multiprocessing (SMP) operating system both increased reliability and extended the availability of timesharing services for users. In addition, maximum real memory size was increased by 25 percent, and timesharing hours were extended to allow unattended service during the night.

As in the past, software was enhanced to meet the needs of the user community. This year's additions include TVEDIT, a new text editor on the DECsystem-10 that uses no command words, and POSTER, an easy-to-use program on the DECsystem-10 that generates customized posters and slides for textual material.

The building renovation program that began two years ago is nearly completed. A new, larger, modern user terminal room with a variety of interactive terminals and a Remote Job Entry (RJE)

terminal was put into operation on the first floor of Building 12A. Efficient and comfortable, the User Area provides an effective work environment and is equipped with adequate power and air conditioning facilities to support the growing needs of users for years to come.

The custom-designed training facility--equipped with sound-insulated walls, carpeting, large work tables, and cushioned chairs to provide a comfortable learning environment--is now being used for Computer Center training classes. Comfort and safety are enhanced by variable lighting that allows illumination for note-taking while the screen area is dimmed, by dust-free chalkless marker boards, and by built-in projection facilities that eliminate the hazard of trailing electrical cords.

This year, the Molecular Graphics System operated by CCB was used to solve structure problems where very little information was available. An algorithm was developed to determine from first principles the shape of RNA molecules in three dimensions. The algorithm successfully reconstructed PHE- and SER-tRNA molecules. Models of the limulus hemocyanin complex were developed from image-enhanced electron microscope data. Using symmetry constraints, the space-filling representation of macromolecular structure was extended to represent structures of several million daltons. The models of several viruses--including adenovirus, the Semliki Forest virus, and polyoma virus--were also constructed.

Future Plans

The coming year will see the next steps in the Computer Center's continuing plans to provide better services at equivalent or reduced costs.

The installation of 64 IBM 3380 disk actuators during early FY83 will complete the total replacement of all hardware comprising the IBM System 370 facility. During the year, the disk drives on the DECsystem-10 facility will be replaced by RP07 drives that have a capacity two and one half times that of the current RP06 drives.

Following the completion of the installation, the major emphasis of the Computer Center staff for FY83 will be directed toward the design and implementation of facilities and procedures to increase system availability. A number of new, realtime performance monitoring tools will be incorporated into the system to permit the early detection of faults or performance deterioration. New problem diagnosis methods and procedures to permit the rapid identification and resolution of problems will be investigated. Steps will be taken to minimize scheduled system shutdowns for dumps, data migration, fix application, equipment installs and maintenance, and to isolate services for improved reliability and availability. Fail soft, back-up, and recovery procedures will be improved to minimize recovery time when failures do occur.

The teleprocessing facilities of the NIH Computer Utility will be expanded and improved to provide additional capacity to support more remote terminal users and to offer new functions and higher speed services. Facilities will be investigated to support a greater variety of terminal types, including word processors, on all services provided by the Computer Utility and to support more convenient methods of switching among services. During the year, the Computer Center will replace its interactive CRT and hardcopy terminals with new, more modern units and a procurement will be initiated to acquire new Remote Job Entry (RJE) workstations.

The Computer Center will invest significant effort in the installation of improved physical and technical security facilities to insure the privacy of user data. Access to the physical plant and computer output boxes will be controlled by an electronic access control system. New software security facilities will permit the 'owner' of sensitive data and programs stored on the Utility to exert more specific levels of control over access to them.

The coming year also will see an emphasis on the development of new self-study training courses for users and the completion of the audiovisual facilities in the new training rooms. In addition to these rooms, the ongoing building renovation program will include construction of offices for the Systems Team and Office of the Chief, CCB, on the second floor of Building 12; the Plotter and Microfiche Units will move to new quarters on the first floor of Building 12A.

Publications

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Office of the Director

Arnold W. Pratt, M.D., Director

Three separate units make up the Office of the Director, DCRT: the **Office of ADP Policy Coordination**, the **Office of Administrative Management**, and the **Office of Scientific and Technical Communication**.

These offices complement the work of the six Laboratories and Branches by:

- coordinating the complex Federal policies and procedures that govern getting and using computers at NIH
- providing general administrative management support for the Division's work
- serving as a central source of information about DCRT activities and about computer-related disciplines.

Office of ADP Policy Coordination

Henry J. Juenemann, Chief

Function and Scope of Work

The Office of ADP Policy Coordination, under the direction of the Assistant Director of the Division, has four closely related functions:

1. It serves as a focus for NIH-wide coordination of Automatic Data Processing (ADP) policy matters.
2. It serves as a central NIH point of contact with the Public Health Service, the Department of Health and Human Services, other HHS Agencies, and the General Services Administration on policy and regulatory questions.
3. It provides the point of contact for those NIH procurement and contracting matters that must be cleared by DCRT prior to procurement or contracting action.
4. It also provides advice and assistance to NIH staff and others concerning the internal operations of DCRT in matters of ADP policy and procurement.

The activities of the Office include:

- advising the Director of DCRT and, through him, the Director of NIH on ADP policy matters
- reviewing and evaluating proposals from NIH B/I/D's for procurements and contracts related to computing and ADP
- directing the development of the annual NIH ADP Plan
- assisting the NIH Division of Management Policy on questions relating to its responsibility for administrative and management computer applications
- representing NIH in PHS and DHHS policy formulation efforts
- working with HHS and GSA staff to obtain necessary approvals for NIH on procurements and contracts, and
- answering inquiries from scientists and administrators who are confused by the whole process.

FY82 Accomplishments

A major set of tasks accomplished during FY82 involved obtaining PHS, HHS, and GSA approval for full recompetition of three contracts under which DCRT supplies the three types of NIH Standard Terminals to users. This required extending the present contracts in order to provide adequate lead time for the reprocurments. It also required six sets of interlocking clearances and three minor and three major solicitation packages. The tasks were accomplished during FY82 in a way that provided continuous terminal support to users of the DCRT-operated NIH computer utility.

During the year, this office reviewed nearly 400 proposals for acquisition of ADP equipment and/or services and commented on approximately 100 research contracts involving ADP. Each was reviewed to ensure that it was justified and was in conformance with PHS, HHS, GSA, and OMB guidelines. Suggestions and assistance were provided to the NIH Procurement Branch and to the various Research Contract Branches as to the most expeditious procurement route to follow. In many cases one or more of the Laboratories and Branches of DCRT assisted by providing expertise to help in the review of technical aspects of the proposals.

In addition, the office was heavily involved in the development of specifications, RFP's, and clearances for a variety of specialized automated systems, including many minicomputers for laboratory use. A contract was awarded for the automation of the NIH Library; implementation of the initial phases of that project is underway. A delegation of procurement authority was obtained from GSA for a long term project to automate the data handling associated with the Division of Research Services' animal breeding program. Preparation of the necessary solicitation package and conduct of the procurement was underway during the latter part of FY82. Likewise, GSA delegations of authority were obtained for the total reprogramming of the National Library of Medicine's MEDLARS system and for the upgrading of the hardware that will be required to develop, test, and operate the new and improved MEDLARS System.

The *Annual ADP Plan* that combines projections of new ADP initiatives and required ADP expenditures for all Bureaus, Institutes, Divisions, and Offices of NIH was completed. It details an NIH ADP program projected to be 75.5 million dollars and 772 work years in FY83 growing to 80.5 million dollars and

788 work years in FY84 and to 83.9 million dollars and 853 work years in FY88. Although the accuracy of the out-year projection must be regarded with caution, the trend of ADP and computing involvement in the scientific and managerial life of NIH is unmistakable.

Future Plans/Trends

FY83 will be marked by major changes in the structure, staffing, and focus of NIH's ADP Policy Coordination function. These changes, the nature of which are not predictable at this writing, should be accomplished during the last quarter of FY82.

Office of Administrative Management

L. Lee Manuel, Chief

Function and Scope of Work

The Office of Administrative Management, under the direction of the Executive Officer, consists of 15 people, organized functionally into three sections: finance, personnel, and general administration. The office serves as liaison between these functions and the NIH Office of Administration, Office of Research Services and with other NIH, PHS, and DHHS offices. It handles a broad range of administrative managerial functions for an NIH research division of almost 300 people.

Fiscal Year 1982 Accomplishments

The Administrative Office processed a variety of procurements and acquired approximately 30 million dollars in supplies and equipment during FY82. Day-to-day management activities conducted by this staff included: procurement purchases and contracts; processing of travel and training requests; administration of property, space, and communications; payroll; and mail/messenger services. In October 1981 the Administrative staff began using the Delegated Procurement System (DELPRO), a subsystem of the NIH Materiel Management System (MMS). This process allows B/I/D personnel to enter and control their own delegated procurement data such as ICO's and ROC's, Repair Orders, reprint orders, FACS book orders, and professional services requests.

Based on a decision by the Director, DCRT, the Budget Office developed budgets at the laboratory level and implemented a reporting system to allow Lab/Branch Chiefs to track actual obligations against their budgets. This has resulted in greater awareness of spending patterns and more accurate recordkeeping. The need for even more detail by the Lab/Branch Chiefs will undoubtedly result in some modifications, but the reporting system has proved to be a valuable management tool. The office also

participated in setting and reviewing rates for Service and Supply Fund data processing activities. This was especially challenging in a year of major equipment transition in the Computer Center.

The Project Control Office continued to process requests for new accounts, register new users, and prepare billing data for the NIH computer facility. The office also successfully completed its major annual update of information on over 10,000 users and 2,000 accounts. Several modifications, including the elimination of some reports, were made to the Project Accounting System.

The Personnel Office processed approximately 400 personnel actions that included promotions, reassignments, temporary appointments, excepted appointments, transfers, and career-conditional appointments. The Department continued to operate under a partial hiring restriction most of the year, making outside recruitment and selection difficult.

A new Departmental performance appraisal system was implemented this year, effective October 1, 1981, as a result of the Civil Service Reform Act of 1978. Personnel Office staff conducted training and orientation for all supervisors and employees on the implementation of the new Employee Performance Management System (EPMS). This massive effort involved 12 separate sessions, each conducted by either the Personnel Officer or the Personnel Management Specialist. The Personnel Officer serves as the coordinator for EPMS and provides assistance to employees and supervisors on a continuing basis.

The writing of new factor evaluation position descriptions in the GS-334-0 series for all computer specializations in DCRT was coordinated by the Personnel Office with the assistance of contract personnel who conducted workshops on the Factor Evaluation System for the 334 series. The Personnel Office staff carried out the classification of these positions.

The Executive Officer and Assistant Director served on a work group with the Director and staff of the NIH Division of Management Policy to prepare a position paper with alternative recommendations for the Director, DCRT, and for the Associate Director for Administration, NIH, concerning the ADP policy functions at NIH. The paper described the functions associated with this process and addressed certain issues that should be resolved.

The Executive Officer also coordinated the preparation of the Annual Research Plan and represented the Division within OD, NIH, as Program Planning Officer. He also served the Division as its international representative to the Fogarty International Center and as its legislative contact with the Division of Legislative Analysis, OPPE, NIH. This required keeping abreast of issues in these

areas and advising the Division's staff as necessary on items that might have an impact on DCRT programs.

A new Full Time Equivalency (FTE) system was implemented to track DCRT employment against NIH-mandated ceilings.

Future Plans/Trends

The OAM will continue its efforts in providing administrative management support to the Division's programs. A new OMB Circular, A-123, titled 'Internal Control Systems' will probably be implemented at NIH during the coming year. This Circular prescribes policies and standards to be followed in establishing and maintaining internal controls in program and administrative activities.

Office of Scientific and Technical Communications

William C. Mohler, M.D., Chief

Functions

The DCRT Office of Scientific and Technical Communications (OSTC), under the direction of the Associate Director, DCRT, includes:

- the DCRT Library, which maintains a high quality collection of materials for use by DCRT and NIH staff and serves as a resource for other libraries;
- the DCRT Information Office, which serves as the focus for providing the NIH community and the professional and lay public with information about DCRT's activities and related applications of computing in biomedical research;
- scientific work in related areas of pattern recognition, multidimensional information processing, and applications to medical decision making.

Scope of Activities

The DCRT Information Office handles the full range of activities of an NIH Information Office. The Information Officer, assisted by a Public Affairs Specialist, answers inquiries, produces and distributes print and audiovisual materials, and arranges briefings for visitors. The office coordinates special events, works with members of the media, and provides advice, assistance, and educational resources on communications for the DCRT staff. It also responds to all Freedom of Information requests coming to DCRT.

A major part of the Information Office program is directed within NIH toward improving an understanding of the Division's work and the application of computing to biomedical research. But the scope of its communications includes Federal agencies, schools, libraries, private industry, medical organizations, representatives of the media, and a wide variety of individual scientists, engineers, other professionals, and lay persons.

The DCRT Library is a fully independent, special library, staffed by the Librarian and a Library Technician. The Library provides a full range of services and has access to a wide variety of online information services and data bases. The collection of monographs, periodicals, and other documents covers subjects related to the work of DCRT. These include computer science, mathematics, statistics, electronic engineering, information science, and management.

The Library supports the work of the DCRT staff and serves as a resource for employees in the rest of NIH. It is an integral part of the Washington area network of special libraries and cooperates with libraries outside the area to share resources. It does this through organizations such as the Interlibrary Users Association of the Washington/Baltimore Area, the Metropolitan Washington Library Council, FEDLINK (a Federal library consortium), and the national OCLC (Online Computer Library Center) network.

The other activities of OSTC derive from the interests of its scientific professionals. They work with other professionals at NIH and with medical and technical groups, both government and private, outside of NIH.

Highlights of FY82

Dr. Prewitt was very active in FY82. She was the leader in organizing two major scientific meetings: MEDCOMP '82, the First International Conference on Medical Computer Science sponsored by the IEEE Computer Society, and the First International Symposium on Medical Imaging and Image Interpretation. Her collaborations with physicians, mathematicians, engineers, and computer professionals led to papers and presentations on medical decision making and on pattern recognition applied to biomedical images. She began an appointment as Stocker Professor of Electrical

Engineering at Ohio University under the aegis of the Intergovernmental Personnel Act.

The DCRT Information Office underwent several changes. In the first quarter, Mrs. Hodges moved to work full time on the needs of the Data Management Branch for informational materials describing their computer systems. Despite this, the Office had another productive year. This is even more noteworthy in light of other assignments undertaken by its staff and new restrictions placed upon public information activities in the general effort to cut costs and improve efficiency throughout the Federal Government.

As part of this effort, the Information Officer, Mrs. Miller, went on detail for four months to the Office of the Assistant Secretary for Public Affairs, DHHS, to assist with several projects involving public affairs and computer expertise:

1. A study in response to OMB Circular M-81-14, 'Federal Information Centers,' for which the Department must develop an implementation plan to consolidate, eliminate, and improve its existing clearinghouses and resource centers.
 2. The systems review process mandated by Public Law 96-511, the Paperwork Reduction Act.
 3. The Department's response to H.R. 4758, which proposes legislation on the government sale of data processing and telecommunications services, and cost recovery of same.
 4. A project to design and implement a data processing system to keep track of Department-wide public affairs budgets and publications, as part of a DHHS Control Plan mandated by OMB Bulletin 81-16, 'Elimination and Consolidation of Government Periodicals and Recurring Pamphlets.'
- During her absence, Mr. Hall handled the office, within the limits of his temporary appointment.

In spite of these constraints, the staff covered the many routine day-to-day activities and provided consultations on a variety of communications services. These included arranging publicity for MLAB courses, assisting in slide production for a presentation of BRIGHT, obtaining contract editorial services for Division staff members, and assisting the DCRT director in responding to administrative requests.

In addition to coordinating, editing, and producing the *DCRT Annual Report*, the Office carried out the following major efforts during the year:

- Printed materials about DCRT activities went to over 6,000 people. To provide current information on DCRT activities, the Office produced complete revisions of the old brochures describing the Laboratory of Applied

Studies and the DCRT Library, and it obtained reprints of *Computers at NIH: Tools for the Advancement of Medicine* and of the DCRT *Fiscal Year 1981 Annual Report, Volume 2*.

- The Office wrote articles for the *NIH Record* and helped other DHHS groups report DCRT activities. The PHS covered WYLBUR in its publication *Future Office*; the Clinical Center and the NIH Audiovisual Branch prepared *NIH Record* articles citing work in DCRT.
- The Division received mention in several private media throughout the year. These included the *SIGBIO Newsletter*, *VoiceNews* (a newsletter on voice technology), *Current Health* (a magazine for high school students), *Sky* (Delta Airlines' in-flight magazine), and *Omni* (a half-hour television science magazine). Film footage of molecular graphics was taken for future use on a CBS television program, *The Body Human*. The Information Office arranged for regional computer voice technology experts to be interviewed on the Illinois public television network.
- The short sound/slide show describing the Division and highlighting each laboratory and branch was completely revised to help brief visitors and orient new employees.
- Work on the DCRT bibliography involved correcting and updating records on over 1,000 scientific papers written by DCRT researchers over the last 12 years.

The Information Officer continued to explore the economics of electronic typesetting. As Chair of the NIH Printing Committee, she advised others on these methods. She also served on the Board of Directors of the Washington chapter of Women in Communications, Inc., a national organization for public relations, journalism, broadcasting, and communications professionals.

The DCRT Library also had a busy year improving service while managing fixed space, budget cuts, and changing technology.

A complete redesign of the Library brochure now helps users more readily locate monographs, documents, journals, and reference materials. New signs made by the Library staff identify shelf areas, sections of the card catalog, and locations for return of materials. The Librarian, Mrs. Chu, compiled the prototype for a series of bibliographies covering specific subject areas of the library's collection.

A fourth online bibliographic reference service provided better coverage for the wide range of technical and scientific needs of users of the Library. The hidden cost to this breadth of coverage is the

time that the Librarian and the Library Technician, Ms. Fiorentino, must spend mastering system updates and the idiosyncracies of the data files and indexing strategies. The Librarian attended the District of Columbia Online Users group meetings to share experiences with such systems and to keep current with new developments in this emerging technology.

Budget restrictions caused a reduction of monograph purchases and a complete review of the list of serial acquisitions. In spite of this, space limitations required continued attention to weeding out less useful materials and to conversions of essential journal holdings to microforms. With the aid of the DCRT Library Committee, a review of the collection led to removal of some 50 monographs, 400 documents, and 200 journal volumes.

A multistage, multiyear project continued to cope with the new Anglo-American Cataloging Rules (AACR2). This effort is complicated by the high cost of computer-based library systems. None yet meets the needs and budget of our small special library. The Library's own computer-based circulation control system continues to perform well at a reasonable cost. For the moment the strategy to approach computer-based cataloging remains use of the OCLC data base to create a machine readable file of items in the collection, edited according to AACR2 and local conventions. These can be produced on tape by FEDLINK at the appropriate time.

Much of the Library's work is aided by the Librarian's active role in professional organizations. She continued as a FEDLINK delegate to the OCLC Users Council and served on the Council's Executive Committee as Council Secretary. She completed the first of two years as a Director on the Executive Board of the District of Columbia Library Association, an organization of some 1,000 Washington area librarians.

Plans

Plans for the coming year will follow the general lines of work in FY82. The current Federal emphasis on control of publications and audiovisual products will offer a significant restraint for providing information about DCRT activities to the NIH community and to the many groups outside NIH that have expressed interest in DCRT work. The continuing trend toward limited budgets in the face of persistent inflation will require efforts to cut costs while maintaining a high level of service in the Library and a high quality of products from the Information Office.

Nevertheless, there is reason to be optimistic for the immediate future. Both the Librarian and the Information Officer have plans to meet these challenges. Dr. Prewitt's appointment to an endowed position at Ohio University will allow her to pursue her work in the coming year without some of the current limits on funds, personnel, and equipment that exist in the Division.

Publications and Presentations

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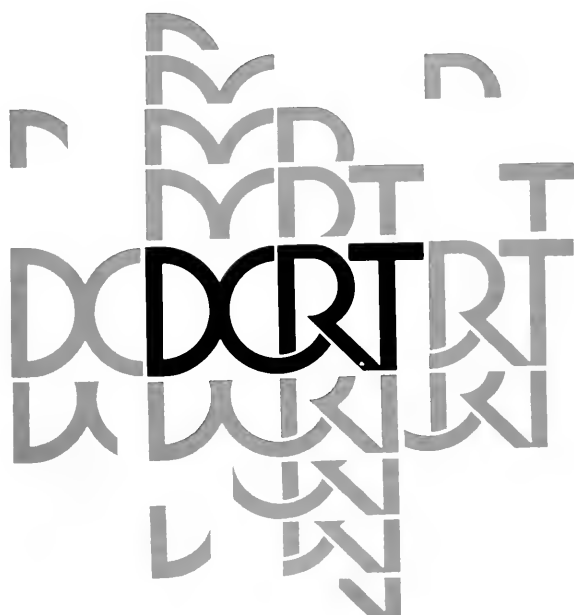


Division of Computer Research and Technology
National Institutes of Health
Bethesda, Maryland 20205

FISCAL
YEAR
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ANNUAL
REPORT

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Foreword

The Division of Computer Research and Technology has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH. DCRT serves as a scientific and technological resource for other parts of PHS, and for other Federal organizations with biomedical and statistical computing needs.

DCRT programs focus on three primary activities: conducting research, developing computer systems, and providing computer facilities.

The fiscal year 1982 annual report describes our work in two volumes:

Volume 1 gives an overview of the work of each group, highlighting the year's accomplishments;

Volume 2 gives details about the projects and activities of each group.

Contents

Computer Systems Laboratory

Clinical Research, Patient Care, Epidemiology.....1
Laboratory Investigation.....3
Program Management and Administration.....4
Biomedical Communications and Conference Support.....5
Computer Research and Technique Development.....5
Research Projects
Computer Support for Flow Microfluorimetry/Cell Sorters (FMF).....5
Cardiac Scintillation Probe.....7
Computerized Radiation Therapy.....8
Medical Intensive Care Unit Patient Monitoring Computer System.....9
Automated Management of Critically Ill Patients.....11
Positron Emission Tomography (PET) Scan Image Analysis in Aging Studies.....11
Computer Assisted Tomography (CAT) Scan Image Analysis in Aging Studies.....13
Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies.....13
Cataract Grading via Computerized Slit-Lamp Image Analysis.....14
Robust Boundary Detection of Necturus Gall Bladder Cells.....15
Rehabilitation Medicine Computer System.....16
Positron Emission Tomography (PET) Facility.....18
Computer Assisted Hematology Morphology Data Handling System.....19
Automated Pulmonary Physiology Testing.....19
Assessment of Tongue Motion During Speech Using Ultrasonic Imaging Techniques.....21
Anesthesia Computer System.....22
Medical Information Technology Project.....23
Molecular Graphics and Sequence Analysis.....24
Computer Analysis of Gel Electrophoresis.....25
Morphometric Analysis of Normal and Neoplastic Tissue Cultures.....26
Virus Structure As Determined by Image Processing of Electron Micrographs.....27
Image Processing of Electron Micrographs.....28
Potentiometric Titration Controller.....29
Metabolic Energy Measurements.....30
Electron Energy Measurements.....30
Electron Microanalysis Facility.....31

Molecular Interactions Laboratory Data System.....33
Californium-252 Plasma Desorption Mass Spectrometer Data System.....34
Distributed Laboratory Data Acquisition and Control System.....34
Image Processing Facility.....36
Analytic Models of Computer System Performance.....37

Laboratory of Applied Studies

Clinical Research and Patient Care.....41
Laboratory Investigation.....42
Computer Research and Development.....42
Research Projects
Statistical Research in Clinical Pathology.....43
Mathematical Models of Binding Equilibria.....44
Mathematical Modeling of Substrate Transport in Physiological Environments.....44
Analysis of Coupled Transport and Biochemical Kinetics.....46
Nonlinear Equations.....48
Numerical Approximation Techniques for the Solution of Reaction-Diffusion Systems in Biology.....50
Monitoring of the CNS in Critically Ill Patients.....51
Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease.....52
Investigation of Hybrid Computing for the Construction of Simulation Models and for the Analysis of Physiologic Signals.....53
Computer Systems for Nuclear Medicine.....53
Computer-Aided Analysis of Electrocardiograms.....54
Computer-based Studies in Ultrasonography.....55
Computer Based Analysis and Image Processing in Electron Microscopy and X-ray and Electron-Loss Spectroscopy.....56

Physical Sciences Laboratory

Summary of Activities.....59

Research Projects

Consulting Services.....60

Studies in Mathematics and Statistics.....61

Theory of Biochemical Separation
Techniques.....61

Correlation Function Spectroscopy/Laser Light
Scattering.....62

Cell Motility and Chemotaxis.....63

Two-dimensional Fourier Transform Nuclear
Magnetic Resonance Spectroscopy.....63

Precision in the Measurement of NMR
Parameters.....64

Theory and Measurement of Intermolecular
Forces.....64

Analysis of Intracellular pH by ³¹P Nuclear
Magnetic Resonance Spectroscopy.....65

Quantitative Analysis of Cell Electronmicroscopy
and Plasma Membranes.....65

Diffusion of Molecules on Cell Surfaces and
Light Scattering from Fluids.....66

Control of Actin Assembly in Nonmuscle
Cells.....67

Computerized Typesetting of Scientific
Papers.....68

Data Management Branch

Clinical Research, Patient Care, Epidemiology.....83

Laboratory Investigation.....85

Program Management and Administration.....86

Biomedical Communications Applications.....87

Computer Research and Technique Development.....88

Computer Center Branch

Summary of Projects.....91

Research Projects

Computer Representation of Virus and other
Macromolecular Assemblies.....93

Office of the Director

Summary of Activities.....95

Research Projects

Electronic Typesetting Methods.....96

Laboratory of Statistical and Mathematical Methodology

Clinical Research, Patient Care, Epidemiology.....72

Laboratory Investigation.....72

Program Management and Administration.....73

Biomedical Communications Applications.....73

Computer Research and Technique Development

Automated Data Processing of Medical
Language.....73

Cluster Analysis.....74

Research Topics in Computer Science.....75

Discrete Mathematics and Applications.....76

Multivariate Statistical Analysis.....77

Linear Methods in Statistics.....78

Non-numerical Programming Techniques and
Applications.....78

Topics in Geometry and Analysis.....80

Computer Systems Laboratory

Alan M. Demmerle, Chief

Clinical Research, Patient Care, Epidemiology

Computer Support for Flow Microfluorimetry (FMF) /Cell Sorters (NCI, NHLBI). This project provides support for the acquisition, display, and analysis of data from four Becton-Dickinson FACS-11 and one Coulter MDADS FMF in NCI and NHLBI. All five systems currently use Digital Equipment Corporation PDP-11 computers with RT-11 single user operating system. CSL is developing an RSX-11M multi-user system to replace RT-11 in some high volume applications. This system will feature an LSI-11 microcomputer (satellite) that will interact independently with the FMF operator during parameter entry and will acquire data and send it to a PDP-11 computer (host) for storage through an interprocessor link.

Cardiac Scintillation Probe (CC, NHLBI). This nonimaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. The system can continuously derive parameters such as LV compliance, ejection fraction, filling and ejection rates, and various temporal relationships. The probe continues to be used to study the effects of nifedipine and verapamil on patients with asymmetric septal hypertrophy. In addition, a new protocol studying drug effects on patients with coronary artery disease was initiated. The probe is also being used to monitor the left ventricle performance of patients in the Medical Intensive Care Unit.

Nuclear Medicine Computer Systems (CC). CSL has continued consultation and support for the imaging systems in the Nuclear Medicine Department, CC, to assess their changing needs and anticipated growth in the new Ambulatory Care Research Facility (ACRF).

In the ACRF the three existing systems were placed in individual scan rooms and a central system was purchased to provide a central viewing station for processed studies, data storage, and increased program development capability. A distributed system was implemented to provide communication between the systems. Investigations using high efficiency camera systems and their potential applications were also initiated.

Computerized Radiation Therapy (NCI). CSL developed a computer system, now in clinical operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from computer assisted tomography to improve radiation treatment planning. This system for external beam treatment planning is based on a generalized 3-D dose field model that covers photon, electron, and neutron beams.

The computer program and most of its clinical implementation has been completed for the photon and electron fields available from the local 6 MV and 12 MV linear accelerators. The current capabilities include interactive simulation of most irradiation techniques devices. The system enables the display of dose distributions computed in several transverse contours and overlaid on corresponding CT scans.

Medical Intensive Care Unit Patient Monitoring Computer System (CC). The dynamic events occurring within the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system. Capabilities of the system include data acquisition and analysis, medical recordkeeping, tabular and graphical data display, and feedback control as required in support of patient care and research protocols.

The facility contains a state-of-the-art catheterization laboratory with flexible computerized physiologic monitoring features, and a high resolution x-ray system with digital subtraction angiography

capability. Of primary interest is the study of the etiology and therapy of septic shock.

Automated Management of Critically Ill Patients (CC). This new research project is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal is the utilization of computer-based instrumentation to aid in the differential diagnosis of disease states, and the implementation of therapeutic modalities through automated technology.

A state variable approach is utilized in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Several alternative methods for closed-loop automated medical interventions are being investigated.

The Biomedical Image Analysis Project (NHLBI, NEI, NCI, NIADDK, NIDR). This project is oriented toward the development of general-purpose algorithms and techniques for image input (including digitization), image enhancement (including contrast enhancement), feature extraction (including edge detection, contour extraction, contour following, contour coordinate compression, and shape and texture analysis), three-dimensional representation, image reconstruction (including Fourier filtering, combining images, symmetrization), and other techniques of image processing and image reconstruction. The capability is used in work with a number of NIH researchers.

Automated ECG Processing (CC). The Clinical Center's Heart Station was automated last year with a computer system that provides for the online acquisition, analysis, storage, and retrieval of diagnostic electrocardiograms. The newest versions of the vendor's turnkey software and diagnostic criteria packages were installed and the system was placed in routine clinical operation. The ECG analysis package will be modified by CSL as necessary to customize the ECG analysis process in order to satisfy NIH requirements.

Rehabilitation Medicine Computer System (CC). This project involves the development of computer techniques in collaboration with the Department of Rehabilitation Medicine of the NIH Clinical Center. CSL has recommended computer techniques to automatically acquire anatomical and performance information, perform calculations, and display the results to the medical staff. The automated techniques include the measurement of body forces (hand and ground reaction forces), electromyograms (electrical activity of the muscle), and body kinematics (the position and angles of the limbs and joints in space and time). The medical staff will enter additional data into a data base with computer

generated forms displayed on a terminal screen, and perform inquiries and generate reports using the accumulated data. A competitive procurement is underway and system installation is targeted for the early spring of 1983.

Positron Emission Tomography (PET) Facility (CC). Various NIH Institutes use the PET Facility of the Nuclear Medicine Department. To meet increased demand for PET scans and analysis, CSL ordered and installed peripherals on the PET computer system to handle the increased data flow. To increase the image data analysis capability, CSL implemented an offline minicomputer system and modified existing image analysis software. In collaboration with Institute scientists, this system was programmed to compute local cerebral metabolic activities with radioactive deoxyglucose utilization.

Computer Assisted Hematology Data Handling System (CC). In February 1982, CSL, in collaboration with the Clinical Pathology Department, CC, completed the design and installation of a microcomputer-based system that allows entry of manual white cell differential, red cell morphology, and platelet estimates. It replaces the old method of manual offline counting and transcription to mark sense cards. A menu-driven CRT display at four user stations is used with a variety of dynamic formats. Data can be compared with automated cell counting results, which are displayed at the top of the screen. Results are then transferred online to the Clinical Pathology Laboratory Computer System via a direct serial communications line.

Automated Pulmonary Physiology Testing (NHLBI). Fully-automated lung static compliance and inspiratory muscle strength procedures are now routinely performed in the Pulmonary Branch's pulmonary physiology/exercise laboratory. Under the control of a MINC 11/03 computer system, data is acquired and analyzed in realtime, with graphical and textual reports produced at the completion of each procedure.

Steady-state treadmill exercise testing has been partially automated. Although data is manually entered, analysis and report generation are fully computerized. Work is in progress to enable automatic realtime acquisition of exercise data with breath-by-breath analysis and thus makes the procedure entirely noninvasive. Once the steady state procedure is successfully implemented, a nonsteady state protocol is planned.

Pulmonary Branch Support (NHLBI). This project assists the Pulmonary Branch in its computer and data processing needs. CSL continued to help

maintain the computer portion of the two Collins automated pulmonary function analyzers. The BRIGHT software package, operating on the DECsystem-10, was identified as one means for managing pulmonary patient data. CSL provided introductory training and helped organize a general scheme to enable investigators to develop and maintain individualized data storage and analysis capabilities using BRIGHT.

Assessment of Tongue Motion During Speech Using Ultrasonic Imaging Techniques (CC). A collaborative effort with the Departments of Rehabilitation Medicine and Diagnostic Radiology, CC, CSL, and the Physical Sciences Laboratory, DCRT, initiated to develop both a system and an analytical technique for realtime ultrasonic imaging of the tongue. Using an existing realtime diagnostic scanner, several normal subjects were scanned during the utterance of specific phonemes. The resultant images were digitized and analyzed for reliability and repeatability. Mathematical techniques are under investigation for describing the patterns of tongue motion obtained. New instrumentation is being evaluated to implement this technique in the new ACRF Speech Lab scheduled for operation in FY83.

Anesthesia Computer System (CC). This is a collaborative effort with the Anesthesiology Service, CC, to evaluate improved instrumentation techniques and to identify and investigate ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring and automated recordkeeping in the operating room. Efforts this year centered on the development of a project plan to guide future work.

Medical Information Technology Project. This project is concerned with the development of better ways to automate the essential physician contribution to the health care record. This year, in collaboration with a practicing dermatologist, we are field testing an ambulatory patient care treatment system. It is designed to help the physician generate patient information and treatment schedules, pharmacy prescriptions, medical and surgical reports, laboratory test orders, and referral letters to other doctors. Interaction with the system consists of high-speed friendly menu selections with many default fields preselected. Because most of the clinical software is table driven, it can be adapted to other clinical care and research environments.

Laboratory Investigation

Molecular Graphics and Sequence Analysis (NIADDK, NCI, NIDR). The sequence of some

regular proteins, together with other structural information such as data from x-ray diffraction, fiber diffraction, electron microscopy, and spectroscopic analysis can be used to evaluate models of the protein structure. Four projects have been using both modeling techniques developed at NIH. We have recently published a new interpretation of the x-ray diffraction data for collagen fibrils. Analysis of cyanogen bromide fragments of keratin filaments are being studied to understand their structure and to compare keratin with other filamentous proteins. Analysis of myosin and streptococcal M proteins is continuing as sequences become available.

Potentiometric Titration Controller (NHLBI). The Potentiometric Titration Controller previously developed by CSL and LCB, NHLBI, has been greatly enhanced by replacing the original spectrophotometer with a rapid scan spectrophotometer (RSS) that is capable of capturing and storing multiple complete optical spectra. As before, the solution potential is established by microcomputer-controlled electric currents, and the amounts of electron transport carriers are determined from spectral data. With the new system, it is possible to acquire scans in milliseconds instead of the 20 to 30 seconds needed by the earlier spectrophotometer. The system is now being used to study the electron transport chain in mammalian mitochondria.

Metabolic Energy Measurements (NHLBI). A microcomputer-based instrument has been designed to study the energy transduction phenomena of respiring membranes. Electrodes interfaced to the microcomputer via an A/D converter allow membrane potential and protonmotive force to be calculated. The computer also monitors a pH electrode and an oxygen-measuring electrode. The oxygen uptake rate of the cellular material is calculated as is the proton extrusion rate and the proton-to-oxygen ratio. Users can observe all quantified parameters on a multipen plotter as they alter the medium of the experiment.

Electron Microanalysis Facility (DRS). CSL is collaborating with BEIB, DRS, to develop an automated electron microanalysis facility consisting of two electron microscopes interfaced to a PDP-11/60 computer system. The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL is designing and implementing the computer system, which will acquire and display the spectra and images resulting from Electron Energy Loss (EEL) and energy dispersive x-ray spectrometry (EDS). This year,

software for acquiring EEL and EDS spectra and EEL, EDS, and electron current signal images was completed. Basic software for displaying this data was also completed. A large data base of empirical x-ray emission and absorption data was compiled and validated, and retrieval software implemented. Software for the analytical spectrometer, and for 'housekeeping' data acquisition and calibration was improved. A user interface for most data acquisition and display functions was designed and implemented.

Electron Microanalysis Computer System (NINCDs). Late in FY81, the Laboratory of Neuropathology and Neuroanatomical Sciences, NINCDs, requested assistance in setting up a minicomputer system to be connected to a JEOL JEM-100CX electron microscope equipped with a Kevex 7000 Analytical Spectrometer, an Energy Dispersive x-ray detector, and an Electron Energy Loss Spectrometer. CSL recommended the purchase of a system compatible with the BEIB Electron Microanalysis Facility so that software developed for that project could be used without modification. A PDP-11/34 was delivered. CSL installed the operating system along with the Kevex 7000 and x-ray emission data base software developed for the BEIB facility.

Microelisa Data Logger (NHLBI). A microprocessor-based instrument has been developed to record data from a Dynatech Microelisa Autoreader, a commercially available spectrophotometer. This special purpose instrument is another variation on CSL's digital cassette data recorder. The instrument receives ASCII data from the Microelisa via an RS232 interface port, edits and formats the data for recording, and writes blocks of data onto a digital cassette tape. The instrument will either be transparent to communications between terminal and modem or, when directed by the operator, will read tape records and transmit the data over a communications line via the modem. Using a STD microprocessor bus has resulted in a more compact instrument requiring less power and less unused circuit board 'real estate' than our previous designs.

Molecular Interactions Laboratory Data System (NHLBI). This microcomputer (PDP-03) data system supervises the acquisition and processing of information from an analytical ultracentrifuge and a circular dichroic spectropolarimeter used in MDB, NHLBI, to investigate the interactions between human lipoprotein subunits. Preprocessed data are transferred to the DECsystem-10 for further analysis under MLAB using predefined procedures invoked by a few simple commands. The results of a study of system performance with very dilute solutions were

presented at the 1982 FASEB meeting in New Orleans. Plans are now underway for the modification of the ultracentrifuge interface to provide greater noise immunity and for the addition of a digital plotter to the system.

Californium-252 Plasma Desorption Mass Spectrometer Data System (NHLBI). After delays caused by hardware design problems, software upgrades, and facilities renovations, both the spectrometer and a data system modeled after one in use at Texas A&M University have been installed and are now functional. This instrument provides NIH the capabilities of mass analysis for compounds difficult or impossible to analyze by other mass spectrometric means. It also extends the range of mass analysis to compounds with molecular weights in excess of 5000.

DLACS Project (NIADDK). An integrated laboratory data acquisition and processing system has been developed for LCP and LMB, NIADDK. The system is configured with thirteen satellites coupled through a local network to a host processor. At each satellite, a dedicated microcomputer system performs data acquisition from and control over an instrument/experiment. Although acquired data files may be stored locally, they are normally transferred via the network to a host storage medium. The local network allows the host storage medium to appear as a virtual storage device to the satellites. The hub of the network, the concentrator, utilizes DMA hardware on all communications links and performs a file store and forward function. Processing software provided at the host allows LDACS data files to be added, subtracted, averaged, smoothed, baseline corrected, integrated, differentiated, multiplied by a constant, or added to a constant. The results may be displayed graphically on a Tektronix terminal, typed at a terminal, printed on the line printer, plotted on an X-Y plotter, or transmitted to the NIH DECsystem-10 for additional processing.

Program Management And Administration

Small Animal Section Data Base Management System (DRS). In FY82, CSL revised and expanded the functional specifications developed in FY81 to generate a Request for Proposals for a small animal data management system for the Small Animal Section (SAS), VRB, DRS. We issued a Sources Sought to test the market for currently operating animal data management systems. Sixteen vendors responded, of which only three had the necessary experience to be evaluated as qualified. The RFP will be issued in the final quarter of FY82. Responses

will be evaluated by early FY83. We anticipate that a contract will be signed in the second quarter of FY83.

Library Automation (DRS). A CSL study performed in FY79 recommended that the NIH Library purchase a commercially available library system. Because none of the available systems could completely satisfy the Library's requirements, the study emphasized system flexibility in order to allow CSL programmers to make modifications and additions to the system. Due to administrative delays the procurement process did not start until late FY81.

During FY82, CSL has been heavily involved in a series of complex contract negotiations occasioned by an early admission from the contractor that work could not be performed in the promised time frame. The period of the contract was eventually extended for several months in return for substantial cost and technical concessions. In addition, CSL is supervising site preparation and providing programming support for conversion and editing of part of the data base not covered by the contract.

Biomedical Communications And Conference Support

Computers in Cardiology Conference. CSL continued its support of the annual International Conference on Computers in Cardiology. The Conference provides a forum for direct interaction and exchange between physicians, computer scientists, and engineers who are involved in various aspects of clinical computer systems in the field of cardiology.

Computer Research And Technique Development

Image Processing Facility. This project is intended to provide a utility to display and analyze digital images. The system will consist of a powerful 32-bit computer with a mixture of medium and high resolution video displays. Also, the system will include a microdensitometer to allow precise digitization of images. The computer and peripherals have been purchased and procurement of the display subsystem is in progress. Site preparation is also underway and completed system installation is forecast for early 1983.

Analytic Models of Computer System

Performance. This new project involves the development of analytic models that can be used to evaluate the performance of computer systems. During the past year, tools for modeling and analyzing computer systems using the graph

theoretic model called Timed Place-Transition (P-T) Nets were developed. A method was developed for evaluating computer system performance with Timed P-T Net models. This method was used to model and analyze the bus arbitration techniques that occur in digital systems. Important upper bounds on the average time a device waits for the bus and the average time the shared bus is not used were derived. In addition, a state variable P-T Net model of the interconnection of two or more microprocessors was developed. This model provides a framework for determining the avoidance of deadlock and the maintenance of throughput in multiple microprocessor systems.

Research Projects

Computer Support for Flow Microfluorimetry/Cell Sorters (FMF)

This project provides PDP-11 computer support at various levels for four Becton-Dickinson FACS II and one Coulter MDADS flow cytometry/electronic cell sorting instruments. Data acquisition is via an NIH designed interface to the computer. Data display and analysis for high sample throughput is the principal system feature. Software currently running under the RT-11 operating system is being converted to function under the RSX-11M operating system in order to allow more sophisticated recordkeeping and more effective support of current and anticipated workloads. New hardware and software capabilities are being added during the conversion effort. Upon completion the RSX System will be installed on the Immunology Branch, NCI computer.

Objectives and Methods: Since FY75 CSL has provided engineering, system integration, and software support necessary to meet the data acquisition, data display, and analysis needs of several investigators using flow cytometry/electronic cell sorting instruments at NIH. Software development and testing is done on a Digital Equipment Corporation (DEC) PDP-11/40 computer system owned by CSL. This allows investigators to have full use of their systems while new software is being developed.

All systems are currently using the RT-11 single-user operating system. The systems allow data collection of up to four parameters on individual cells. Typically these are light scatter, two frequencies of fluorescence, and cell volume. The data can be collected in single parameter or correlated dual parameter modes. Data analysis and display programs allow the experimenter to produce various statistics and hard copy displays from the acquired

data. The displays include three-dimensional pictures, contour maps, and vertical slice sections.

Progress in FY82: In FY82, CSL continued to support FACS-II/PDP-11/34 systems for I, NCI; LP,NCI; EA,H; EEB, NCI; and a Coulter MDADS/ PDP-11/34 system for MO,NCI.

The major effort in FY82 was continuing the conversion of RT-11 programs to run under the RSX-11M multi-user operating system as well as adding functionality to these programs. The RSX-11M system is initially being developed for one system in order to provide more effective support of current and anticipated workloads and more sophisticated data acquisition and recordkeeping functions. This system will be available to other NIH FMF sites as needs require after its implementation in the Immunology Branch, NCI.

It was decided in FY81 to replace the DEC VT-11 graphics display device with a Tektronix 4025 and to support this terminal on the RSX system. A new graphics software package was needed to drive the 4025 initially for the RSX-11M system. In conjunction with the T4025, a contract was negotiated with Electronic Data Systems, Inc., to assist CSL personnel in developing software packages for displaying graphs on any terminal that is capable of performing Tektronix 4010 style graphics.

All four of the major FMF data display and analysis programs were rewritten to run under RSX-11M, using the new graphics software package and the Tektronix 4025 terminal that was delivered in the first quarter of FY82. Several minor improvements to the RT-11 display and analysis programs were made in FY82 in order to accommodate immediate needs of our supported users.

The new data acquisition system environment consists of a PDP-11 host computer running RSX-11M and up to eight LSI-11 based satellites, each running RT-11, connected to the host via an interprocessor link.

Data acquired by a satellite is usually sent over the link and stored at the host site (Remote Storage Mode). However, in the event of a link failure, data is stored at the satellite site (Local Storage Mode). The satellite link software is common to all satellites, but distinct from the host link software. Together, the host and satellite link software provides file transfer capability.

The development of the link software was completed in FY82 and the hardware for a complete satellite system has been acquired. The acquisition portion of the LSI-11 acquisition system has been written and is being tested.

An important feature of the satellite system is the ability to create a 'laboratory notebook' as a permanent hard copy rather than continuing this as a manual task as in the existing PDP-11/34 system. This 'notebook' concept is an integral part of the software that provides interaction with the operator via a DEC VT-100 terminal. Special features of the VT-100 are used to provide the operator with an easy-to-use single screen menu. Errors are reported in detail on the terminal screen. This interactive software was completed in FY82.

During the third quarter of FY82, the DEC PDP-11/40 computer system used for development of software for CSL-supported FMF systems was relocated to Building 12A from Building 10. CSL has also responded to many external requests and has provided copies of the interface hardware schematics, software, and documentation to FMF sites in the U.S., Europe, and Australia.

Proposed Course: In the forthcoming year, CSL plans to complete the first RSX-11M based FMF system and LSI-11 based data acquisition system and put them into operation at the I,NCI facility. If resources permit, the RT-11 software will be rewritten to use the T4025 graphics terminal as a replacement for the VT-11. CSL will also continue to support existing RT-11 based FMF sites at NIH.

DISCIPLINARY SOURCE INFORMATION (SOURCE PROJECT NUMBER (DO NOT use this space))		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NCI	PROJECT NUMBER Z01 CT0005-03 CSL
PERIOD COVERED February 1, 1981 to September 30, 1982			
TITLE OF PROJECT (80 characters or less) Computer Support for Flow Microfluorimetry/Cell Sorter (FMF)			
NAMES, LABORATORY AND INSTITUTION ABBREVIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
PI: R. J. Romanoff Computer Specialist CSL, DCR OTHERS: R. Fico Electronics Engineer CSL, DCR E. S. Lovelander Computer Aid CSL, DCR S. O. Sharrow Chemist I, NCI A. R. Schultz Chief, Processor Design Section CSL, DCR			
COOPERATING UNITS (if any) I, NCI; LP, NCI; EEB, NCI; MO, NCI; EA, NHLBI			
LAB/BRANCH Computer Systems Laboratory			
SECTION Processor Design Section			
INSTITUTE AND LOCATION DCR, NIH, Bethesda, MD 20205			
TOTAL MANPOWER: 2.2		OTHER: 2.2	
CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER			
<input type="checkbox"/> (a) WOUNDS <input type="checkbox"/> (a) INTERVIEW			
SUMMARY OF WORK (200 words or less - underline keywords)			
This project provides PDP-11 computer support at various levels for four Becton-Dickinson FACS II and one Coulter MDADS flow cytometer/electronic cell sorting instrument. Data acquisition is via an NIH-designed interface to the computer. Data display and analysis for high sample throughput is the principle system feature. Software currently running under the RT-11 operating system is being converted to function under the RSX-11M operating system in order to allow more sophisticated recordkeeping and more effective support of current and anticipated workloads.			

PS-4040
(Rev. 2-61)

Cardiac Scintillation Probe

Background and Objectives: The development of the cardiac scintillation probe is a continuation of CSL's collaboration with the Nuclear Medicine Department, CC, and the Cardiology Branch, NHLBI. Originally this collaboration resulted in the development of a noninvasive cardiac imaging technique known as ECG-gated scintigraphic angiography. In addition to visualizing global LV cardiac function, the images produced by this technique can be processed to produce a time-activity curve that represents changes in ventricular volume over a cardiac cycle. This time-activity curve (LV volume curve) can be used to calculate various parameters of cardiac function such as ejection fraction, peak ejection rate, peak filling rate, and their temporal relationships. The imaging technique has been used with great success to characterize various cardiac related diseases. However, if the images are not required, then this time-activity curve could be generated by a much smaller and simpler system using a single small NaI detector and microcomputer system. In 1977 CSL began the development of a cardiac scintillation probe system, which could produce this time activity curve. The system is easily transportable and allows continuous monitoring of cardiac function at the

bedside or other location in the Clinical Center outside the Nuclear Medicine Department.

Methods: The system consists of a 3-inch diameter NaI scintillation probe, probe electronics, microcomputer system, and display. The system is programmed to acquire scintillation data from the probe, process the data, and plot and display various parameters of left ventricular (LV) function. This nonimaging, ECG-gated probe, when used in conjunction with ventricular catheterization, permits simultaneous quantification of the variation of LV volume and LV pressure. Parameters such as LV compliance can be continuously monitored. In the catheterization laboratory, pressure-volume measurements are used to study the effects of drugs on patients with various heart diseases.

Progress in FY82: This year the probe continued to be used in the catheterization laboratory to study the effects of nifedipine and verapamil on patients with asymmetric septal hypertrophy (ASH). The pressure volume data from these studies were transferred to the PDP-10 system and software was written to analyze the data to determine additional parameters to assess the effects of these drugs. The verapamil studies have been concluded. The pressure-volume data has provided information to help understand the positive effects of the drug in this particular disease.

A new protocol studying drug effects on patients with coronary artery disease was initiated. As with the ASH study the data is being analyzed to determine the parameters that best characterized the effects of the drug.

Results of the drug intervention studies indicated changes in ventricular parameters previously not used. Nine studies were designed and performed in order to quantitate the limitations of techniques in measuring these parameters.

The Medical Intensive Care Unit, CC, has started to perform ECG-gated Scintigraphic studies. Because using the Pho/Gamma camera on a routine basis at the bedside is difficult, software was written on the HP system to use the probe in this application.

Significance to Biomedical Research: Nuclear Medicine techniques provide a relatively noninvasive procedure to access left ventricular function. The cardiac scintillation probe permits this capability to be used for clinical research studies at the bedside and in the catheterization laboratory. The pressure volume relationship produced by the probe system allows the effects of drugs to be quantitated in a manner not before possible.

DISSEMINATION STATEMENT INFORMATION (EXHIBIT) PROJECT NUMBER (On NSF and other forms) PROJECT NUMBER		NCI, DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NCI-DCI INTERNATIONAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00051-03 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982				
TITLE OF PROJECT (No characters or less) Cardiac Scintillation Probe				
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: H. G. Ostrow Electronics Engineer CSL, DCRT OTHERS: S. L. Allen Medical Research Analyst CSL, DCRT S. Bacharach Physicist NW, CC M. Green Physicist CB, NHLBI R. Bonow Cardiologist CB, NHLBI D. Rosen Cardiologist CB, NHLBI				
COOPERATING UNITS (if any) Nuclear Medicine, CC, Cardiology Branch, NHLBI				
LAB/BRANCH Computer Systems Laboratory				
SECTION Processor Design Section				
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205				
TOTAL MANHOURS 1.0		PROFESSIONAL 1.0		OTHERS
CHECK APPROPRIATE BOXES (1)				
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEUTRON				
<input type="checkbox"/> (d) X-RAYS <input type="checkbox"/> (e) INTERVIEW				
SUMMARY OF WORK (500 words or less - underline keywords) CSL continued the development of its Cardiac Scintillation Probe System begun in 1977. This nonimaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. By simultaneously measuring LV volume and LV pressure, parameters such as LV compliance can be continuously monitored. In addition to such measurements as ejection fraction, filling and ejection rates, and temporal relationships. This year the probe continued to be used to study the effects of nifedipine and verapamil on patients with asymmetric septal hypertrophy. In addition, a new protocol studying the drug's effects on patients with coronary artery disease was initiated. The probe is also being used to monitor the left ventricle performance of patients in the Medical Intensive Care Unit. The pressure-volume relationship produced by the probe system allowed the effects of drugs to be quantitated in a manner not possible before. New software has been added to permit the system to be easily used on a routine basis by Clinical Center personnel. Development is continuing on increasing the detection efficiency of the probe and in quantifying the limitation of the technique.				
PHS-2042 (Rev. 2-81)				

Proposed Course: Development activities in response to new applications are expected to continue. CSL will investigate making the probe and camera systems compatible. Making the systems compatible to the extent possible will reduce the resources required to support the probe system and allow new capabilities developed for the camera systems to be implemented quickly on the probe system.

Computerized Radiation Therapy

CSL has developed a computer system, now in clinical operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from ultrasound or computer assisted tomography to improve radiation treatment planning. This system for external beam treatment planning is based on a generalized 3-D dose field model that covers photon, electron, and neutron beams.

Both the computer program and most of its clinical implementation have been completed for the photon and electron fields available from the local 6 mv and 12 mv linear accelerators. The current capabilities include interactive simulation of most irradiation techniques, including the effects of most beam modifying devices. The system enables the display of dose distributions computed in several transverse contours and overlaid on corresponding CT or ultrasound scans.

Background and Objectives: To develop and implement a generalized system for computer-assisted radiation treatment simulation.

Methods Employed: The dose field model developed by Jan van de Geijn was implemented in RSX-11M FORTRAN and experimentally tested to cover irregularly shaped beams as well as irregularly-shaped shielding blocks. A facility has been developed that enables the computation and display of dose distributions in planes perpendicular to the beam axes.

Progress in FY82: The capabilities of the graphics input system, the use of CT and ultrasound images in addition to mechanically-obtained patient contours, and the color display system have been further expanded. Eight user terminals and two DeAnza 10 5000 color display systems have been added to allow the PDP 11/70 computer system to be used for treatment planning and system development.

Major Findings: The system, although continuing to be expanded, is in routine use for clinical treatment planning. In comparison to other existing systems, it offers high speed computation and display of

complete dose distributions in multiple slices superimposed on CT or ultrasound images, including effects of wedge filters, irregular shielding blocks, and diaphragm rotation. Several modes of display are available.

Proposed Course: Future plans include: implementation of the beam's eye view option for regular and irregular electron fields, extension of the current software package to include point source (seed) calculation, and extension of the capabilities to compute and display dose distributions in sagittal, coronal, and beam's eye view sections of the patient on an interactive basis.

Publications:

van de Geijn, J., Chien, I-Chu, Cheng, C. P., and Fredrickson, H.A.: A Unified 3-D Beam Model for External Beam Dose Distributors. *Proceedings of the VIII International Conference on Computers in Radiotherapy*, Tokyo, Japan, 1980.

INTERDISCIPLINARY INFORMATION EXCHANGE PROJECT NUMBER (DO NOT USE THIS SPACE)		N.C.I. DEPARTMENT OF HEALTH AND HUMAN SERVICES FOUNTAIN HEAD, MARYLAND NATIONAL CANCER INSTITUTE NATIONAL RADIATION RESEARCH PROJECT		PROJECT NUMBER Z01 CT00052-03 CSL	
PERIOD COVERED October 1981 to September 30, 1982					
TITLE OF PROJECT (40 characters or less) Computerized Radiation Therapy					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT					
PI:		H. Fredrickson		Computer Systems Analyst CSL, DCRT	
OTHERS:		J. Van de Geijn		Head, Radiation Physics Automation Section ROB, DCRT, NCI	
		D. Syed		Head, Systems Design Section CSL, DCRT	
		E. Glatstein		Chief, Radiation Oncology Branch ROB, DCRT, NCI	
		B. Fraass		Staff Fellow ROB, DCRT, NCI	
		L. Freeman		Computer Programmer CSL, DCRT	
COOPERATED UNITS (if any) Radiation Oncology Branch, NCI					
LABORATORY Computer Systems Laboratory					
SECTION Systems Design Section					
INSTITUTE AND LOCATION DCRT, NCI, Bethesda, MD 20205					
TOTAL MANUSCRIPTS		1.1		PROJECT RESULTS 1.1	
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) REFINER <input checked="" type="checkbox"/> (a) MINDS <input checked="" type="checkbox"/> (a2) INTERVIEWS (SUMMARY OF WORK (DO NOT WRITE OR TYPE - UNDERLINE HYPHEN))					
CSL has developed a computer system, now in clinical operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from ultrasound or computer assisted tomography to improve radiation treatment planning. This system for external beam treatment planning is based on a generalized 3-D dose field model that covers photon, electron, and neutron beams.					
Both the computer program and most of its clinical implementation have been completed for the photon and electron fields available from the local 6 mv and 12 mv linear accelerators. The current capabilities include interactive simulation of most irradiation techniques, including the effects of most beam modifying devices. The system enables the display of dose distributions computed in several transverse contours and overlaid on corresponding CAT or ultrasound scans.					
PIS-6040 (Rev. 2-81)					

Medical Intensive Care Unit Patient Monitoring Computer System

The dynamic events occurring within the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system. Capabilities of the system include online data acquisition and analysis, medical recordkeeping, tabular and graphical data displays, and feedback control, as required in support of patient care and research protocols. Elements include a minicomputer-based Patient Data Management Subsystem, a Software Development Subsystem, and a Medical Mass Spectrometer Subsystem.

The facility also contains a state-of-the-art catheterization laboratory that includes a flexible computerized Vascular Research Subsystem, with physiologic waveform processing features, and a high-resolution x-ray system with digital subtraction angiography capability.

Of primary interest is the utilization of the Medical Intensive Care Unit's computer systems in the study of the etiology and therapy of septic shock.

Background and Objectives: The Medical Intensive Care Unit (MICU), which is administered by the Department of Critical Care Medicine in the Clinical Center, receives critically ill patients from clinical programs of NIH. The MICU comprises a five-bed ward area, a pair of isolation beds, and a vascular research laboratory. The research goals of this unit include the development of techniques for automated patient monitoring and noninvasive measurements of the cardiovascular and respiratory systems. In addition, catheterization studies are performed as necessary to obtain data that are available only through invasive methodology.

Working with Clinical Center staff, CSL contributed to the engineering design of the intensive care unit. CSL also undertook the specification, procurement, and installation of the bedside patient monitoring equipment and the four computer systems:

1. a Patient Data Management System used for automatically monitoring patient variables, manually entering patient data, retrieving information online, and keeping medical records;
2. a Vascular Research Subsystem used for acquiring and processing cardiovascular pressure waveforms, measuring cardiac output, displaying measured results online, and generating a cardiac catheterization report;
3. a Software Development Subsystem used for developing software for the above described systems; and

4. a Medical Mass Spectrometer Subsystem used for monitoring both the patient airway gases and the gases delivered by the patient's respirator at all seven MICU beds.

The first three systems were purchased from the Hewlett-Packard Corporation and all use identical minicomputers. The Chemetron Corporation manufactures the microcomputer-based mass spectrometer system. This year, additional subsystems have been incorporated within the MICU complex.

Major Findings: The automation of the MICU has aided the medical staff by managing the large amount of data needed for the care of the critically ill patient, performing desired calculations, and allowing measurements that would not otherwise be possible.

Progress in FY82: Modifications to the Vascular Research Subsystem were completed to allow the data generated to be collected by the Patient Data Management Subsystem's computer, in addition to the Vascular Research Subsystem's computer. A mobile noncomputerized Vascular Research Subsystem was added to the MICU to allow bedside monitoring with research quality instrumentation. This mobile subsystem also interfaces to the Patient Data Management Subsystem's computer.

In order to provide pulmonary function monitoring for the critically ill population within the MICU, a Collins Pulmonary Function Testing Subsystem was integrated into the MICU. This microprocessor-based subsystem contains the spirometer and gas analyzers necessary for the calculation of pulmonary function parameters, such as vital capacity and lung volumes, and for the generation of flow-volume loops.

A Hewlett-Packard Respiratory Research Subsystem was obtained to provide for the computation of pulmonary mechanics parameters, such as work of breathing and lung compliance and resistance. This subsystem also utilizes airway pressure and flow transducers to develop pressure-volume loops, in addition to flow-volume loops.

A Microprocessor-Controlled Arrhythmia Monitoring Subsystem was added to the Nurses' Station in the MICU to provide for the central monitoring of cardiac arrhythmias. This display station provides an electrocardiogram memory and provides simultaneous hard copy records of the electrocardiogram and arterial pressure waveforms, as aids in the detection of transient arrhythmias.

In order to supplement the electrocardiographic and cardiac catheterization data descriptors of cardiac function, a Hewlett-Packard Microprocessor Controlled Ultrasound Imaging Subsystem was installed in the MICU. This subsystem provides multiformat displays of cardiac structure and allows the visualization of intracardiac abnormalities. In addition, this Ultrasound Imaging Subsystem interfaces to the Software Development Subsystem to allow sophisticated image processing with NIH-developed programs.

A Cardiac Probe, which was developed jointly by CSL staff and the Clinical Center's Nuclear Medicine Department, is being adapted for use in the MICU. This device provides left ventricular volume data by counting gamma ray induced scintillations, after the administration of injectable radioisotopes. Software is being completed to allow data from the Cardiac Probe to be collected, analyzed, and displayed utilizing the Software Development Subsystem's computer.

A Philips X-ray Imaging System was installed within the MICU Catheterization Laboratory. CSL staff assisted in the specification and supervision of catheterization laboratory alterations necessary for system installation. Shielding was installed to protect the MICU computer room from exposure to electromagnetic interference from the x-ray system's generator and power supplies. The x-ray Imaging System includes a Computerized Digital Vascular Imaging Subsystem that provides the capability for digital subtraction angiography. A video switching device added to the Vascular Research Subsystem allows video displays produced by the Vascular Research Subsystem, the Patient Data Management Subsystem, and the Digital Vascular Imaging Subsystem to share a single Philips Video Monitor.

Significance to Biomedical Research: This project is focused on the application of multifaceted diagnostic modalities to clinical research and the care of the critically ill patient. Any new developments made on this project will benefit many users of automated systems, as well as patient care and clinical research within the MICU at NIH.

Proposed Course: Future efforts will center on hardware and software modifications necessary to enhance the system's ability to support patient care and research protocols. Possible modifications to the primary Patient Data Management Subsystem include the addition of urine output measurement scales and the computerization of fluid infusion therapy utilizing existing microprocessor-controlled infusion pumps.

CRITICAL CARE MEDICINE INFORMATION EXCHANGE PROJECT NUMBER (40 max. char. incl. space) PERIOD COVERED TITLE OF PROJECT (40 characters or less) NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: OTHERS: R. L. Martino, Ph.D. L. W. Freeman S. L. Huntley COOPERATING UNITS (if any) LAB/BRANCH SECTION INSTITUTION AND LOCATION TOTAL MATERIALS OTHER APPROPRIATE DATA(S) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a) MINDS <input type="checkbox"/> (b) INTERVIEWS SUMMARY OF WORK (200 words or less - underline keywords) The dynamic events occurring within the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system. Capabilities of the system include online data acquisition and analysis, medical recordkeeping, tabular and graphical data displays, and feedback control, as required in support of patient care and research protocols. Elements include a minicomputer-based Patient Data Management Subsystem, a Software Development Subsystem, and a Medical Mass Spectrometer Subsystem. The facility also contains a state-of-the-art catheterization laboratory that includes a flexible computerized Vascular Research Subsystem, with physiologic waveform processing features, and a high-resolution x-ray system with digital subtraction angiography capability.	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES OFFICE OF BIOMEDICAL RESEARCH PROJECT PROJECT NUMBER Z01 CM0054-03 CSL
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CRITICAL CARE MEDICINE INFORMATION EXCHANGE PROJECT NUMBER (40 max. char. incl. space) PERIOD COVERED TITLE OF PROJECT (40 characters or less) NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: OTHERS: J. E. Parrillo M.D. N. McClaris, Sc.D. COOPERATING UNITS (if any) LAB/BRANCH SECTION INSTITUTION AND LOCATION TOTAL MATERIALS OTHER APPROPRIATE DATA(S) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a) MINDS <input type="checkbox"/> (b) INTERVIEWS SUMMARY OF WORK (200 words or less - underline keywords) This research project is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal is the utilization of computer-based instrumentation to aid in the differential diagnosis of disease states and the implementation of therapeutic modalities through automated technology. A state variable approach is utilized in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Empirical clinical data and real-time monitored values are utilized in model validation. Several alternative methods for closed-loop automated medical interventions are being investigated.	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES OFFICE OF BIOMEDICAL RESEARCH PROJECT PROJECT NUMBER Z01 CM0099-01 CSL
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Automated Management of Critically Ill Patients

This research project is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal is the utilization of computer-based instrumentation to aid in the differential diagnosis of disease states and the implementation of therapeutic modalities through automated technology.

A state variable approach is utilized in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Empirical clinical data and realtime monitored values are utilized in model validation. Several alternative methods for closed-loop automated medical interventions are being investigated.

Background and Objectives: Noninvasive diagnostic and therapeutic techniques generally involve the application of sophisticated electronic technology and mathematical modeling techniques to the detection of pathophysiologic states. Particularly interesting and important problems involve cardiovascular disorders that give rise to low output syndrome.

There is no singular cause for this syndrome, and therefore effective therapy requires the differential diagnosis of numerous contributory disturbances in cardiovascular homeostasis. Effective therapy principally involves the administration of one or more fluids and/or drugs in a critical care unit environment.

Methods Employed: In order to accomplish the goal of developing systems capable of assisting in the medical management of a critically ill patient on a closed-loop basis, it will be necessary to develop validated models. Calculated physiologic parameters will be compared to measured physiologic data as the patient's response to the selected therapy progresses.

A mathematical formulation of the relevant subsystems will be developed for a patient in a critical care unit setting. This includes the modeling of three principal subsystems: Pharmacokinetics, Drug/Receptor Interactions, and Cardiovascular Dynamics.

Progress in FY82: An extensive literature search and a formal analysis were performed on the three major relevant subsystems. The literature search indicated that these three areas have previously been treated as distinct and unconnected problems. There has been little effort to combine them in a manner suitable for addressing the problem proposed.

The mathematical formulations necessary to describe these systems are being finalized. Particular care is being paid to the selection of variables so that the subsystem models will couple in a physiologically sound as well as a computationally efficient manner.

Significance to Biomedical Research: The use of automated systems in the implementation of therapeutic protocols within a critical care unit adds a new treatment modality and will have a major effect on protocol design. It will afford improvements in protocol design for patient care, clinical drug trials, and the study of the etiology and therapy of specific disease entities. In addition, the automation of therapeutic interventions, as proposed, will significantly expand the clinical and research data bases.

Proposed Course: Following the development of the mathematical formulation of the three major subsystems, these subsystems will be implemented in software on the DCRT Central Computer Facility. The software will be utilized in a simulation mode to analyze actual patient data, and to generate recommendations for therapy along with predicted physiologic data values.

Existing critical care protocols will be investigated to identify those components in which automated therapeutic modalities can easily be accommodated, within the framework of this research effort. An important aspect to be evaluated is the risk to the patient versus the realizable benefits.

Selected protocols will be implemented utilizing the closed-loop techniques developed in this project, with the objective of carrying out controlled clinical trials and quantitatively evaluating their effectiveness.

Positron Emission Tomography (PET) Scan Image Analysis in Aging Studies

Procedures for transporting Positron Emission Tomography (PET) Scan and Computer Assisted Tomography (CAT) Scan images from the NIH Clinical Center to the DCRT Image Processing Facility have been established. An interactive computer procedure for delineating anatomical areas of interest on a CAT scan and computing metabolic activity from the corresponding area on the related PET scan has been developed. Improved methods for establishing external coordinates to align corresponding PET and CAT scans continue to be explored.

Background and Objectives: Positron Emission Tomography (PET) scanning performed in the Nuclear Medicine Department of the NIH Clinical Center provides a spatially-sequenced series of images of regional cerebral glucose metabolism in man. The Laboratory of Neurosciences of the National Institute on Aging wishes to incorporate PET scanning technology in the study of diseases associated with aging. The initial goal of this project is to delineate brain substructures represented in spatially sequenced Computer Assisted Tomography (CAT) scan images and to determine metabolic activity in these substructures from corresponding spatially sequenced PET scan images.

Methods Employed: Computer Assisted Tomography (CAT) Scan and Positron Emission Tomography (PET) Scan images are transported from the NIH Clinical Center to the DCRT Image Processing Facility via magnetic tape. An analyst trained in neuroanatomy aligns associated CAT and PET Scan images by means of reference markers seen on both images. These markers are provided by a head-holding device worn by the subject during CAT and PET scanning. The analyst then 'draws' contours around regions of interest on the CAT Scan. The computer determines corresponding regions on the PET Scan and computes metabolic activity in that region of the brain.

Progress in FY82: Radiation-to-glucose conversion equations were finalized and further investigation of a suitable head-holder to provide reference markers external to the brain continued. Image processing software is close to completion. A project entitled 'Computer Assisted Tomography (CAT) Scan Image Analysis in Aging Studies' closely related to this work was started and is reported in this *Annual Report*.

Significance to Biomedical Research: It is anticipated that this work will provide a basis for evaluating the utility of PET scanning in studying diseases associated with aging. Successful implementation of an external coordinate system should provide for accurate anatomical region designation via higher resolution CAT scan images to measure physiological processes from corresponding lower resolution PET scan images.

DISSEMINATION STATEMENT (FOR INFORMATION PURPOSES) PROJECT NUMBER (FOR MD AND THIS SERVICE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT000083-02 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (IN characters or less) Positron Emission Tomography (PET) Scan Image Analysis in Aging Studies		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: J. M. DeLeo Computer Systems Analyst CSL, DCRT OTHERS: S. I. Rapoport Chief LN, NIA		
COOPERATING UNIT (if any) Laboratory of Neurosciences (LN), NIA; Nuclear Medicine Department (NM), GC; Diagnostic Radiology (DR), CC		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION NCRT, NIH, Bethesda, MD 20205		
TOTAL MAN/HR: 1	PROFESSIONAL: 1	OTHER: 1
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input checked="" type="checkbox"/> (a) MINDS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline key words) Procedures for transporting Positron Emission Tomography (PET) Scan and Computer Assisted Tomography (CAT) Scan images from the NIH Clinical Center to the DCRT Image Processing Facility have been established. An interactive computer procedure for delineating anatomical areas of interest on a CAT scan and computing metabolic activity from the corresponding area on the related PET scan has been developed. Improved methods for establishing external coordinates to align corresponding PET and CAT scans continue to be explored.		

PHC-640
(Rev. 2-61)

DISSEMINATION STATEMENT (FOR INFORMATION PURPOSES) PROJECT NUMBER (FOR MD AND THIS SERVICE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT000086-01 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (IN characters or less) Computer Assisted Tomography (CAT) Scan Image Analysis in Aging Studies		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: J. M. DeLeo Computer Systems Analyst CSL, DCRT OTHERS: M. Schwartz Medical Staff Fellow LN, NIA S. I. Rapoport Chief LN, NIA		
COOPERATING UNIT (if any) Laboratory of Neurosciences (LN), NIA; Diagnostic Radiology (DR), CC		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION NCRT, NIH, Bethesda, MD 20205		
TOTAL MAN/HR: 0-3	PROFESSIONAL: 0-3	OTHER: 1
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input type="checkbox"/> (a) MINDS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline key words) An interactive image analysis computer procedure to measure various parameters from Computer Assisted Tomography (CAT) scans of the human brain has been designed and implemented on the DCRT Image Processing Facility.		

PHC-640
(Rev. 2-61)

Computer Assisted Tomography (CAT) Scan Image Analysis in Aging Studies

An interactive image analysis computer procedure to measure various parameters from Computer Assisted Tomography (CAT) scans of the human brain has been designed and implemented on the DCRT Image Processing Facility.

Background and Objectives: This new project has been initiated to study changes in the human brain structure during normal aging and during brain disease processes associated with aging by means of measurements made from Computer Assisted Tomography (CAT) scans of human brains.

Methods Employed: CAT scans are transported to the DCRT Image Processing Facility via magnetic tape. Through interactive analysis of the CAT scan images, an investigator is able to obtain a wide variety of descriptive measurements such as sizes and attenuation values of brain substructures and percent composition of white matter, grey matter, and cerebral spinal fluid.

Progress in FY82: Software was developed to determine the following measurements from CAT Scans of the human brain:

- 1) Bicaudate Index
- 2) Ventricle/Brain Area Ratio
- 3) Width of Ventricles
- 4) Percentage composition of CSF, white matter and gray matter
- 5) Cortical measurements
- 6) Sylvian Fissure
- 7) Interhemispheric Fissure
- 8) General Length and Area measurements

Using this software, measurements were made on scans of several normal subjects.

Significance to Biomedical Research: This quantification methodology will greatly augment visual interpretation of brain CAT scans. It may provide a deeper understanding of brain structure changes during normal aging and disease processes. It is also possible that this work will produce new diagnostic tools.

Proposed Course: Further refinement of the software is planned. A study to determine morphological brain changes related to aging will be conducted.

Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies

A computerized methodology for analyzing autoradiographic spot images associated with recombinant DNA bacterial colonies has been developed in collaboration with scientists in NCI. This system represents a unique refinement in a method to directly identify cloned DNA sequences complementary to messenger RNA that are developmentally or hormonally induced.

Spot density measurements are computed from digitized images produced via microdensitometry. These measurements are corrected for variability in exposure and local background, calibrated to hybridization standards, and normalized for comparison purposes. The system provides a variety of graphical and tabular output that effectively summarizes experimental results and identifies significant induced hybridization events.

Background and Objectives: NCI scientists have been refining techniques to identify cloned DNA sequences complementary to messenger RNA that are developmentally or hormonally regulated. This refinement has led to a methodology that produces autoradiographic spot images representative of the amount of hybridization. The objective of this project is to provide an automated procedure for a quantitative analysis of these images.

Methods Employed: Cloned bacteria are grown on agar in microtiter wells, transferred to filter paper, and hybridized to end-labeled mRNA or cDNA probes. Autoradiographs of the filters are digitized and the density of each spot relative to background is established by means of CSL-developed image processing software operational on the DCRT Evans and Sutherland PDP-11/70 computer system. Compensation for variations in background, film exposure conditions, and hybridization are included in the methodology. A variety of graphical output including scatter diagrams, histograms, and listings is provided.

Progress in FY82: Software development was completed and several experiments were conducted. Two papers are in preparation. The first paper discusses both the application of this system to analyzing the in vivo response of rat liver to glucocorticoids, as well as the application to other biological systems. The second paper will describe the computerized image analysis methodology and procedure in detail.

Significance to Biomedical Research: The methodology developed allows quantitative hybridization studies on a large number of sequences. Earlier qualitative assessment of autoradiographic spot images is now superseded with automated procedures yielding more accurate, more reproducible data. Computer graphic presentation of results greatly facilitates identification of significant experimental events.

Proposed Course: Additional experiments are planned. It is anticipated that the methodology developed here will be discovered to have applicability to other areas of biomedical research, as demonstrated by inquiries from other NIH biomedical research investigators.

DISSEMINATION DESIGN: INFORMATION EXPANSION PROJECT NUMBER (Do not use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE OFFICE OF INTRAMURAL RESEARCH PROJECTS	PROJECT NUMBER Z01 CT000084-02 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982 TITLE OF PROJECT (40 characters or less) Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: J. M. DeLeo Computer Systems Analyst CSL, DCRT OTHERS: Floyd Taub Research Associate LR, C Brad Thompson Section Chief LR, C		
COOPERATING UNITS (if any) Laboratory of Biology (LB), C		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
FACILITY AND LOCATION DCRT NIH, Bethesda, MD 20205		
TOTAL MATERIALS 0.3 PROFESSIONAL OTHER		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
<input checked="" type="checkbox"/> (a1) WINDS <input type="checkbox"/> (a2) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) A computerized methodology for analyzing autoradiographic spot images associated with recombinant DNA bacterial colonies has been developed in collaboration with scientists in NCI. This system represents a unique refinement in a method to directly identify cloned sequences complementary to messenger RNA that are developmentally or hormonally induced. Spot density measurements are computed from digitized images produced via microdensitometry. These measurements are corrected for variability in exposure and local background, calibrated to hybridization standards, and normalized for comparison purposes. The system provides a variety of graphical and tabular output that effectively summarizes experimental results and identifies significant induced hybridization events.		

PHS-5540
(Rev. 2-61)

Cataract Grading via Computerized Slit-Lamp Image Analysis

A new interactive image analysis procedure for analyzing and comparing slit-lamp camera images of human eye lenses has been developed and implemented on the DCRT Image Processing System. This procedure features television camera image digitization, interest area delineation by means of a flexible oval template, data calibration and standardization, and computation of a variety of statistical measurements for descriptive and comparative purposes. Also, an experiment has been designed to analyze the contribution to measurement variance due to photographic procedure, film and film processing, digitization, and analyst judgment factors.

Background and Objectives: A major problem for cataract researchers has been the lack of an objective, reproducible, in-vivo cataract classification scheme. Subjective classification methods are currently depended upon. With the tremendous variability in the morphology of cataracts, it is difficult to rely on such methodology either in survey works or in longitudinal studies. Development of an objective cataract grading scheme is seen as a high priority item among cataract researchers.

Methods Employed: Photographs of human eye lenses obtained from Topcon and Zeiss slit-lamp cameras are digitized via microdensitometry or television signal quantitation. Resulting digitalized images are transported via magnetic tape to the DCRT Image Processing System for interactive analysis. The image analyst first defines and positions an oval window template over the area of interest using dials and then points to a 5-band calibration strip (an integral part of the image) using a graph-pen. A histogram distribution of the pixel values within the template is formed, scaled, calibrated, and processed to generate various statistical measurements used to describe and compare images. Colored isodensitometric representations of the eye lens may be displayed. Time-spaced photographs of an individual patient may be processed to produce an historical summary of lens opacity changes over time. This is viewed to be useful as an epidemiological tool for advancing our understanding of the cataract disease process, as well as in evaluating the effectiveness of therapeutic protocols such as the administration of anticataract drugs.

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT WRITE IN THESE SPACES)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH PROJECT		PROJECT NUMBER 201 CT00085-02 CSL	
PERIOD COVERED October 1, 1981 to September 30, 1982					
TITLE OF PROJECT (60 characters or less) Cataract Grading via Computerized Slit-Lamp Image Analysis					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI: J. M. DeLeo Computer Systems Analyst CSL, DCRT OTHERS: R. O. Sperduto M.D. BE, NEI					
COOPERATING UNITS (if any) Office of Biometry & Epidemiology (BE), NEI Division of Ophthalmology, Harvard Medical School					
LAB/BRANCH Computer Systems Laboratory					
SECTION Systems Design Section					
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205					
TOTAL MANUSCRIPTS		PROFESSIONALS		OTHER	
0-1		0-1			
<input type="checkbox"/> (a) HUMAN SUBJECTS		<input type="checkbox"/> (b) HUMAN TISSUES		<input type="checkbox"/> (c) NEITHER	
<input type="checkbox"/> (a) WRITERS <input type="checkbox"/> (a) INTERVIEWERS					
SUMMARY OF WORK (200 words or less - underline keywords)					
A new interactive image analysis procedure for analyzing and comparing slit-lamp camera images of human eye lenses has been developed and implemented on the DCRT Image Processing System. This procedure features television camera image digitization, interest area delineation by means of a flexible oval template, data calibration and standardization, and computation of a variety of statistical measurements for descriptive and comparative purposes. Also, an experiment to analyze the contribution to measurement variance due to photographic procedure, film and film processing, digitization, and analyst judgment factors has been designed.					

PHS-5040
(Rev. 2-78)

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT WRITE IN THESE SPACES)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH PROJECT		PROJECT NUMBER 201 CT00087-01 CSL	
PERIOD COVERED October 1, 1981 to September 30, 1982					
TITLE OF PROJECT (60 characters or less) Robust Boundary Detection of Necturus Gall Bladder Cells					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI: J. M. DeLeo Computer Systems Analyst CSL, DCRT OTHER: K. Spring Research Physiologist LKEM, NHLBI					
COOPERATING UNITS (if any) LKEM, NHLBI					
LAB/BRANCH Computer Systems Laboratory					
SECTION Systems Design Section					
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205					
TOTAL MANUSCRIPTS		PROFESSIONALS		OTHER	
0-2		0-2			
<input type="checkbox"/> (a) HUMAN SUBJECTS		<input type="checkbox"/> (b) HUMAN TISSUES		<input type="checkbox"/> (c) NEITHER	
<input type="checkbox"/> (a) WRITERS <input type="checkbox"/> (a) INTERVIEWERS					
SUMMARY OF WORK (200 words or less - underline keywords)					
A robust boundary detection algorithm for automated planimetry of Necturus gall bladder cells has been designed to enhance an existing methodology that computes cell volume change histories from video images of cells visualized in a light microscope.					

PHS-5040
(Rev. 2-78)

Major Findings in FY82: The new interactive image analysis system, which produces descriptive measurements and colored isodensitometric images from slit-lamp camera images of human eye lenses, is fully operational and easy to use. Measurement variance due to image analyst techniques seems to be insignificant. Calibration and standardization procedures should considerably reduce variance due to film, film processing, and digitization factors. The largest potential source of variance is in the quality control exercised by the photographer. This factor requires further study.

Significance to Biomedical Research: Development of an objective cataract grading scheme is seen as a high priority item among cataract researchers.

Proposed Course: A vigorous analysis of variance is planned after adequate study and improvement of image capture methodology. Use of supplemental views, such as frontal and retroillumination views, is being considered.

Robust Boundary Detection of Necturus Gall Bladder Cells

A robust boundary detection algorithm for automated planimetry of Necturus gall bladder cells has been designed to enhance an existing methodology that computes cell volume change histories from video images of cells visualized in a light microscope.

Background and Objectives: Epithelial cells of Necturus gall bladder regulate their volume after a change in osmolality of their bathing solution. The Laboratory of Kidney and Electrolyte Metabolism, NHLBI, has developed a computerized methodology for time-tracking cell volume changes through interactive planimetry of video images of cells visualized in a light microscope. The Computer Systems Laboratory has been requested to develop a specialized robust cell boundary detection algorithm to enhance overall throughput processing efficiency.

Methods Employed: The specialized robust cell boundary detection algorithm conceived operates as follows:

1. The investigator points to the center of the cell.
2. Opacity values are collected along 72 rays emanating from the center. The rays are of fixed length and 5 degrees apart.
3. Each ray of opacity values is processed as follows:

- Scale opacity values (0 to 255).
- Accept a single minimum as a tentative edge point.
- Confirm edge point by scaled gradient and localized texture parameters if necessary.

4. Check neighboring pairs of tentative edge points, rejecting pairs that fail the test.
5. Attempt to specify missing edge points by step 3 applied over a narrower segment of the ray as determined by radii of a certified near neighbor edge point and a priori data specifying expected edge point radii lower and upper range values as a function of the angular distance to the nearest ray having a certified edge point.
6. Sequentially connect the edge points.
7. Compute the enclosed area.
8. Repeat steps 1 to 7 over all cell slices to obtain the required volume.

Significance to Biomedical Research: Application of quantitative light microscopic techniques to study cell volume changes due to fluid and ion transport in living epithelial tissues has already proven to be a powerful and effective research tool. An accurate, efficient, robust cell boundary detector algorithm would greatly improve upon the utility efficiency and throughput speed of this methodology.

Proposed Course: It is planned to implement, test, and refine the robust cell boundary detector algorithm described above on the DCRT Image Processing Facility. Upon successful development, consideration will be given to alternative approaches for implementing the algorithm in production mode.

Rehabilitation Medicine Computer System

This project involves the development of computer techniques in collaboration with the Department of Rehabilitation Medicine of the NIH Clinical Center. CSL has recommended computer techniques that can be used to automatically acquire anatomical and physiological information from patients, perform the required calculations on the data obtained, and display the necessary results to the medical staff. The automated techniques include the measurement of body forces (hand and ground reaction forces), electromyograms (electrical activity of the muscles), and body kinematics (the position and angles of the limbs and joints in space and time). An Automated Biomechanics Laboratory System that provides these measurements will be purchased in late FY82. The computer part of the system will allow the medical staff to enter patient and staff data into a data base with computer-generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data. In FY83, the physical space will be designed to accommodate this system in a new area of the Clinical Center.

UNIVERSITY OF CALIFORNIA, SAN DIEGO PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF REHABILITATION MEDICINE	PROJECT NUMBER Z01 CD00081-02 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (DO NOT EXCEED 100 CHARACTERS)		
Rehabilitation Medicine Department Computer System		
NAMES, LAST NAMES AND INITIALS, AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT		
PI:	R. L. Martino	Electronics Engineer CSL, DCRT
OTHERS:	M. D. Jarrett W. Schneiderwind N. L. Gerber	Expert, Biomechanical Engineering RM, CC Chief, Physical Therapy Service RM, CC Chief, Rehabilitation Medicine Dept. RM, CC
SUPERFUNDING UNIT: (if any)		
Rehabilitation Medicine Department, Clinical Center		
LABORATORY Computer Systems Laboratory		
CITY Systems Design Section		
ADDRESS AND LOCATION DCRT, NIH, Bethesda, MD 20805		
TOTAL MATERIALS: 0.5 PROFESSIONAL: 0.5 OTHER:		
CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) NORMAL TISSUES <input type="checkbox"/> (c) RESEARCH		
<input type="checkbox"/> (d) WOUNDS <input type="checkbox"/> (e) INTERVIEW		
SUMMARY OF WORK (DO NOT EXCEED 1000 CHARACTERS) This project involves the development of computer techniques in rehabilitation medicine in collaboration with the Department of Rehabilitation Medicine of the NIH Clinical Center. CSL has recommended computer techniques that can be used to automatically acquire anatomical and physiological information from patients, perform the required calculations on the data obtained, and display the necessary results to the medical staff. The automated techniques include the measurement of body forces (hand and ground reaction forces), electromyograms (electrical activity of the muscles), and body kinematics (the position and angles of the limbs and joints in space and time). An Automated Biomechanics Laboratory System that provides these measurements will be purchased in late FY82. The computer part of the system will allow the medical staff to enter patient and staff data into a data base with computer generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data. In FY83, the physical space will be designed to accommodate this system in a new area of the Clinical Center.		

PHS-0402
(Rev. 2-81)

Background and Objectives: The Department of Rehabilitation Medicine provides physiatric evaluation and treatment, physical therapy, occupational therapy, and speech therapy for NIH Clinical Center patients referred by Institute physicians. In addition, it develops various indices to evaluate these services. This department supports the efforts of, and collaborates with, Institute physicians engaged in research relevant to physical rehabilitation medicine. It also initiates both clinical and basic research independent of Institutes in the rehabilitation of mentally and physically handicapped individuals.

In support of these goals, CSL is developing a computer system. Initially, the department will use the system for the following three projects:

1. The Automated Biomechanics Laboratory: a laboratory that will be used to automatically measure the position of the limb segments in space, the forces in the lower limbs, and the electromyographic signals from the muscles in the limbs;

2. The Hand Dynamometer Instrument: a device that will be used to measure the magnitude and direction of the forces in the hand and to develop clinical tests to diagnose the mechanical and functional status of the hand, arm, and shoulder;

3. The Physical Therapy Quality Assurance System: a data base system that will be used to assess medical staff effectiveness in providing the types of patient care needed, determine staff workload and scheduling, and identify areas for clinical research for the Physical Therapy Service.

Progress in FY82: During the past year, CSL determined the instrumentation and computer requirements for the Department of Rehabilitation Medicine. A considerable amount of specialized instrumentation is needed to perform the required automated measurements. This includes: five motion cameras with light sources that are used to acquire the spatial coordinates of anatomical points on the patient's body with reflective markers, force plates that are used to measure patient ground reaction force, and hard wired or telemetry electromyogram acquisition equipment that is used to measure patient muscle activity. CSL prepared a Request for Proposals for an Automated Biomechanics Laboratory System that will be used to obtain the necessary transducers, instrumentation, and computer hardware and software.

The Physical Therapy Quality Assurance Data Base System was initially implemented on a small computer system. It will be transferred to the larger computer that is purchased with the biomechanics laboratory system. The Biomedical Engineering and Instrumentation Branch of NIH's Division of

Research Services continued development of the hand dynamometer instrument.

Also, during the past year, a collaboration was initiated with the Gait Analysis Laboratory, Department of Orthopedic Surgery, Children's Hospital Medical Center and Harvard Medical School. In the future, computer programs, patient data, and engineering and medical expertise will be exchanged with this group.

Significance to Biomedical Research: The computer system will be used with arthritic, orthopedic, and neurological patients and with amputees in order to evaluate drug therapy, orthotic and prosthetic devices, and medical interventions. It will also be used as a teaching tool to help these patients learn to function with their disability in an efficient manner. Many hospitals in the United States are presently establishing automated biomechanics and gait analysis laboratories. Therefore, any new developments made on this project will benefit users of these automated systems, as well as patient care and clinical research within the Department of Rehabilitation Medicine at NIH.

Proposed Course: The Department of Rehabilitation Medicine expects to purchase an Automated Biomechanics Laboratory System during the coming year. As the Department is moving to a new location in the Clinical Center, the new area will be designed to accommodate the cameras, force plates, EMG equipment, computer hardware, and patient measurement area.

Also, during the coming year, a study will be done to determine the type of force plate that will best meet the measurement requirements of the Department. Comparisons will be made between small modular versus large force plates and piezoelectric versus strain gauge force plate transducers. In addition, methods for accurately determining the velocity and acceleration of anatomical points from acquired motion data will be investigated including the required camera resolution and frame rate and digital differentiation techniques.

Positron Emission Tomography (PET) Facility

The PET facility of the Nuclear Medicine Department is used to collect and analyze images of the human brain for diagnosis and scientific research. The facility includes a PET Scanner that receives data consisting of gamma emissions from patients and a minicomputer system that operates the scanner, reconstructs the data into cross-sectional slices, and performs other analysis. The facility also includes an offline minicomputer system having an image array processor and color display that is used to interactively perform numerous image enhancement and analysis functions. Various NIH Institutes use this facility to research the aging process, schizophrenia, epilepsy, and other brain functions and disorders.

Background and Objectives: In late FY81, the Nuclear Medicine Department requested assistance in improving their PET computer facility. At that time, the PET facility was receiving increased usage by various Institutes and had recently lost some of its technical staff. Our goal was to improve the existing system's hardware and software, to establish guidelines for collecting and storing patient data, and to provide an image analysis system that could be readily operational.

Progress in FY82: To improve scan data flow and acquisition, we purchased and installed larger disks, a tape drive, and a floating point unit. To improve image data analysis, we purchased the offline minicomputer system and installed and modified image analysis software provided by NIMH. We also programmed the analysis system to compute local cerebral metabolic activity with radioactive deoxyglucose utilization.

Proposed Course: NIH will be purchasing new PET scanners and there will be increasing demand for image analysis and for the storage and retrieval of large quantities of data. We will analyze these future demands and recommend appropriate solutions.

OFFICE ORIGIN: SCIENCE INFORMATION LABORATORY PROJECT NUMBER (GS-WF- and THIS NUMBER)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00100-01 CSL
PERIOD COVERED: October 1, 1981 to September 30, 1982 TITLE OF PROJECT (80 characters or less): Positron Emission Tomography (PET) Facility		
NAME(S), LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: A. J. Pashayan Computer Specialist CSL, NCRT OTHERS: W. L. Rizzo Electronics Engineer CSL, NCRT R. M. Kessler, M.D. Head, Positron Emission Tomography Section NM, CC		
COOPERATING UNITS (if any): Nuclear Medicine, Clinical Center		
LAB/BRANCH: Computer Systems Laboratory		
SECTION: Systems Design Section		
INSTITUTE AND LOCATION: NCRT, NIH, Bethesda, MD 20205		
TOTAL MANTELS: 1.9 PROFESSIONAL: 1.8 OTHER:		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEWS		
SUMMARY OF WORK (500 words or less - underline keywords) The PET facility of the Nuclear Medicine Department is used to collect and analyze images of the human brain for diagnosis and scientific research. The facility includes a PET Scanner which receives data consisting of gamma emissions from patients and a minicomputer system that operates the scanner, reconstructs the data into cross-sectional slices, and performs other analysis. The facility also includes an offline minicomputer system having an image array processor and color display that is used to interactively perform numerous image enhancement and analysis functions. Various NIH Institutes use this facility to research the aging process, schizophrenia, epilepsy, and other brain functions and disorders.		

PHS-60402
(Rev. 2-81)

OFFICE ORIGIN: SCIENCE INFORMATION LABORATORY PROJECT NUMBER (GS-WF- and THIS NUMBER)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00096-01 CSL
PERIOD COVERED: October 1, 1981 to September 30, 1982 TITLE OF PROJECT (80 characters or less): Computer Assisted Hematology Morphology Data Handling System		
NAME(S), LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: D. C. Songco Electronics Engineer CSL, NCRT OTHERS: L. Wang Electronics Engineer CSL, NCRT J. A. Ronlon, M.D., Ph.D. Staff Physician CP, CC A. Faust Programmer CP, CC E. W. Lundy Technologist CP, CC B. L. Meigs Chief Technologist CP, CC		
COOPERATING UNITS (if any): CPD, CC		
LAB/BRANCH: Computer Systems Laboratory		
SECTION: Project Development Section		
INSTITUTE AND LOCATION: NCRT, NIH, Bethesda, MD 20205		
TOTAL MANTELS: .8 PROFESSIONAL: .8 OTHER:		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEWS		
SUMMARY OF WORK (500 words or less - underline keywords) Cell morphology evaluation is a major component of the workload of the Hematology Service of the Clinical Pathology Department, CC. Manual white cell differential counting is the predominant method of analyzing white cell morphology. Previously, technologists performed manual differentials and recorded the data on mark sense cards for later entry into the Clinical Pathology Laboratory Computer (CPLC). This approach led to transcription errors, turnaround time lags, and inefficient use of technologist time. The goal of this project was to design and develop an alternative method of handling the cell morphology evaluation.		

PHS-60402
(Rev. 2-81)

Computer Assisted Hematology Morphology Data Handling System

Cell morphology evaluation is a major component of the workload of the Hematology Service of the Clinical Pathology Department, CC. Manual white cell differential counting is the predominant method of analyzing white cell morphology. Previously, technologists performed manual differentials and recorded the data on mark sense cards for later entry into the Clinical Pathology Laboratory Computer (CPLC). This approach led to transcription errors, turnaround time lags, and inefficient use of technologist time. The goal of this project was to design and develop an alternative method of handling the cell morphology evaluation.

Background and Objectives: CSL, in collaboration with the Clinical Pathology Department, CC, has developed a computer-assisted hematology morphology data handling system with the following characteristics: 1) allows direct entry of manual differentials, red cell morphology, and platelet estimates; 2) displays Coulter automated cell counting data for comparison; and 3) links in realtime to the CPLC.

Progress FY82: System development and installation was completed this year.

The technologists were involved in the human factors design of the system including specifying cell types, screen and keyboard layout, procedure definition, and 'help' and system messages. The acceptance and use of the system was both immediate and enthusiastic. Based on an average daily workload of 230 analyses, the system has decreased the manpower requirements by 50%, changed turnaround time for release of certified results from hours to minutes, and reduced transcription time and errors.

A Digital Equipment Corporation (DEC) LSI-11 microcomputer with dual floppy disk drives was used, with four VT100 CRT terminals as user stations. Extensive use of DEC forms software was made to allow flexibility in redefining screens and nomenclature. The system is linked to the CPLC via a direct 1200-baud serial line. The user responds to menus at each stage of the procedure. Help messages are available at any time providing online instruction and verification of procedures.

Proposed Course: Because the present system is already used to capacity, it will be necessary to add or replace hardware and software in order to add additional tasks. Plans are now underway to increase the capability of the present system by using

cartridge disk drives and modifying the system software or upgrading from RT-11 to the more powerful RSX11-M operating system. If this is done, local data storage would be available for a morphology quality control program. Composite lists of platelet counts versus platelet estimates could be generated. Additional user stations could be added if the workload increased. This expansion is, however, predicated on the availability of financial and manpower resources.

Publications:

Donlon, J.A., Wang, L., Lundy, E., Wages, B., Faust, A., Songco, D.C.: A Computer Assisted Hematology Morphology Data Handling System. *Symposium on Computer Applications in Medical Care*, 1983 (in press).

Automated Pulmonary Physiology Testing

Procedures such as exercise testing, pulmonary compliance, and muscle strength have been found successful for evaluating pulmonary function. By exercising a patient on a treadmill and gradually increasing the workload (i.e., speed and incline), the physician can better assess cardiopulmonary disease, which in its early stages generally does not manifest itself under physical exertion. In order to help the physician perform these procedures more effectively, a microcomputer system has been developed to enable automated realtime collection, analysis, and display of pulmonary compliance and inspiratory muscle strength data. Steady-state treadmill exercise testing has been only partially automated. Although data is manually entered, data analysis and report generation are fully computerized. Work is in progress to enable automatic realtime acquisition of exercise data with breath-by-breath analysis. The breath-by-breath technique allows determination of the anaerobic threshold noninvasively, without the need for arterial catheterization. The anaerobic threshold is used as a measure of an individual's 'fitness.' Patient data is stored on a local disk data base for future reference.

Background and Objectives: Physicians monitor pulmonary parameters during exercise to better assess pulmonary function and to diagnose pulmonary dysfunction that only manifests itself under physical exertion. Procedures such as pulmonary compliance and inspiratory muscle strength also give insight into respiratory function.

Until last year, pulmonary treadmill exercise testing was performed manually at NIH. Data were written down and later entered into a programmable calculator for determination of results. Additional summary statistics and a final report were prepared by hand. Inspiratory muscle strength and pulmonary compliance measurements, done in the same lab, likewise were performed manually.

In order to speed both exam and data analysis time, and to improve accuracy, these procedures were automated with a microcomputer system.

Methods Employed: The microcomputer system is a DEC MINC-11/03 (Modular Instrument Computer) containing an LSI-11 microprocessor, 32K words of memory, auxiliary disk storage, and analog-to-digital and digital-to-analog conversion capability. There is also a video graphics display, a keyboard console, a hard copy unit for printing the video display, and a line printer.

In determining pulmonary compliance, transpulmonary pressure (the difference between alveolar pressure, i.e., mouth pressure with mouth shutter closed, and esophageal pressure, as measured by a balloon transducer swallowed by the patient) and lung volume (measured with a wedge spirometer) are determined by the computer as the physician repeatedly closes a mouth shutter throughout a patient's inhalation or exhalation. A graphical plot of the data and an exponential least squares curve fit of the data is then produced to aid in evaluating the 'stretchability' of the patient's lungs.

During the steady state treadmill procedure, the computer monitors expired volume and flow via a Tissot spirometer and pneumotach, respectively, as the patient is subjected to stepped increases in exercise, each time starting from a resting state. Expired oxygen, carbon dioxide, and nitrogen concentrations are monitored via a Perkin-Elmer mass spectrometer gas analyzer. Traditionally, in order to determine the patient's anaerobic threshold (i.e., point where the body begins to rely heavily on anaerobic metabolism and produce lactic acid), the patient is catheterized in order to obtain arterial blood samples at each steady state level. Acid/base and gas concentrations are determined offline by a blood gas analyzer from a sample of the patient's arterial blood, and entered at the keyboard. Pulmonary volumes, flows, and oxygen consumption--a measure of how hard the patient actually works to perform a given level of exercise--are then calculated.

When one has the capability to automatically monitor air flow and expiratory gas concentrations in realtime, the anaerobic threshold can be determined noninvasively without the need for blood pO₂ obtained from arterial catheterization. Anaerobic threshold is determined from measures of exhaled O₂, CO₂, and respiratory quotient. Breath-by-breath analysis also allows the performance of nonsteady state exercise testing, where the patient is subjected to continuously increasing levels of exercise. This methodology provides a more dynamic picture of the patient's cardiopulmonary performance.

Progress in FY82: The MINC computer system is now used routinely to perform the static pulmonary compliance and inspiratory muscle strength procedures. The graphics capability of the MINC VT-105 console terminal was found to fall short of the lab's needs due to the one 'Y' per 'X' plotting limitation. As a result, a Retrographics VT-100 terminal was procured, providing Tektronix compatible bit-mapped raster graphics capability. Using a CSL graphics package, all pulmonary graphics routines were rewritten for Retrographics compatibility.

Throughout the year, several programs were written to aid pulmonary personnel in the analysis and organization of data obtained from other areas of the pulmonary clinical and research service.

Work continued on fully automating the treadmill exercise system. However, a change in clinical priorities re-directed efforts towards the development of a breath-by-breath steady state exercise system rather than simply automating the technique currently performed. Completion of this goal is planned for the end of FY82.

Proposed Course: Once the breath-by-breath steady state exercise procedure is completed, the system will be adapted to perform a nonsteady state procedure as well. Although there are now no immediate plans to add additional procedures to the system, having developed a general purpose tool for pulmonary data collection, new procedures or modified techniques can be easily incorporated into the existing protocol. For example, the computer may enable closed loop control of treadmill speed.

By monitoring heart rate and dynamically varying treadmill speed in response to heart rate changes, it should be possible to apply a more constant workload to the patient, thus leading to more stable results. In addition to the potential for performing new physiology procedures, additional mathematical analyses can be applied to the data in order to gain further insight into a patient's pulmonary function.

Publications:

Nadel, L.D.: Automated Pulmonary Analysis by an Online Microcomputer. In Nair, S. (Ed.): *Computers in Critical Care and Pulmonary Medicine* (in press).

Nadel, L.D.: Breath-to-breath Pulmonary Exercise Testing Using an Online Microcomputer. First IEEE Computer Society International Conference on Medical Computer Science, Computational Medicine (MED-COMP'82), Philadelphia, September 25, 1982.

Keogh, B., Gadek, J., Price, D., Nadel, L., and Crystal, R.: Remarkable Similarities in Exercise Gas Exchange Parameters in Markedly Disparate Diseases: Comparisons Between Idiopathic Pulmonary Fibrosis and 1-Antitrypsin Deficiency. *American Review of Respiratory Disease* 125: 157, April 1982.

Assessment of Tongue Motion During Speech Using Ultrasonic Imaging Techniques

This project is directed at developing a system capable of ultrasonically imaging the tongue in realtime. In addition to obtaining and integrating the necessary hardware, mathematical techniques must be identified and developed to analyze and describe images of continual tongue motion. Thus far, the tongues of several normal subjects have been imaged using a realtime ultrasonic body scanner in conjunction with a videotape recorder. Anatomical features of interest, as the subject vocalizes specific phonemes, are extracted using a graphic tablet followed by preliminary computer analysis. Efforts are presently being devoted to identifying and developing mathematical techniques for analyzing and describing the patterns of continuous tongue motion. Once we complete an evaluation of the ultrasonic scanners commercially available, we plan to purchase and build where necessary the hardware required to implement this technique in our new speech laboratory, scheduled for operation in FY83.

Background and Objectives: Speech investigators have traditionally used radiographic methods for studying tongue motion during speech and swallowing. These techniques, however, are somewhat cumbersome and are not suitable for general screening, diagnosis, or therapy due to the

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLISHED TO SERVICE NOTES OF INTERDISCIPLINARY RESEARCH PROJECT	PROJECT NUMBER Z01 CT00055-03 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Automated Pulmonary Physiology Testing		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: L. D. Nadel, Ph.D. Staff Fellow PDS, CSL, DCRT OTHERS: R. A. Keogh, M.D. Expert PB, TR, NHLRI R. S. Placido Chief, Project Development Section CSL, DCRT		
COOPERATING UNITS (1-4)* Pulmonary Branch, NHLRI		
LAB/BRANCH Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANPOWER PROFESSIONAL: 1 OTHER: 1		
ONION APPROXIMATE BUDGET (a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEUTRON		
(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEUTRON		
(a) WINDUPS (b) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Procedures such as exercise testing, pulmonary compliance, and muscle strength have been found successful for evaluating pulmonary function. By exercising a patient on a treadmill and gradually increasing the workload (i.e., speed and incline), the physician can better assess cardiopulmonary disease, which in its early stages generally does not manifest itself except under physical exertion. In order to help the physician perform these procedures more effectively, a microcomputer system has been developed to enable automated realtime collection, analysis and display of pulmonary compliance and inspiratory muscle strength data.		

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLISHED TO SERVICE NOTES OF INTERDISCIPLINARY RESEARCH PROJECT	PROJECT NUMBER Z01 CT00054-01 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Assessment of Tongue Motion During Speech Using Ultrasonic Imaging Techniques		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: L. D. Nadel, Ph.D. Staff Fellow CSL, DCRT OTHERS: B. C. Sontes, Ph.D. Chief of Speech-Language Pathology Dept. of Rehabilitation Med., CC T. H. Shawker, M.D. Chief of Ultrasonic Imaging Dept. of Diagnostic Radiology, CC M.L. Stone, Ph.D. Consultant, Speech Pathology Dept. of Rehabilitation Med. G. H. Weiss, Ph.D. Chief, Physical Sciences Laboratory PSL, DCRT		
COOPERATING UNITS (1-4)* Department of Rehabilitation Medicine, CC; Dept. of Diagnostic Radiology, CC; PSL, DCRT		
LAB/BRANCH Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANPOWER PROFESSIONAL: 0.25 OTHER: 0.25		
ONION APPROXIMATE BUDGET (a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEUTRON		
(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEUTRON		
(a) WINDUPS (b) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) This project is directed at developing a system capable of ultrasonically imaging the tongue in realtime. In addition to obtaining and integrating the necessary hardware, mathematical techniques must be identified and developed to analyze and describe images of continual tongue motion. Thus far, the tongues of several normal subjects have been imaged using a realtime ultrasonic body scanner in conjunction with a videotape recorder. Anatomical features of interest, as the subject vocalizes specific phonemes, are extracted using a graphic tablet followed by preliminary computer analysis. Efforts are presently being devoted to identifying and developing mathematical techniques for analyzing and describing the patterns of continuous tongue motion. Once we complete an evaluation of the ultrasonic scanners commercially available, we plan to purchase and build where necessary the hardware required to implement this technique in our new speech laboratory, scheduled for operation in FY83.		

harmful effects of x-rays. It is hoped that the development of an ultrasonic system for visualizing lingual function and performance will prove valuable for the general screening and diagnosis of speech pathology. Used as a tool for biofeedback, such a system might be of assistance in helping a patient to correct speech difficulties. As one learns more of the details of tongue motion in swallowing and speech, this imaging system may be of potential value in the fields of neurology and dentistry.

Methods Employed: Using an existing realtime ultrasonic diagnostic body scanner (ATL), several normal subjects were scanned during the utterance of specific phonemes. The resultant images were photographed and digitized using a graphic tablet interfaced to a DECsystem-10 computer. The data was statistically analyzed for reliability and repeatability. Although mathematical techniques for describing the patterns of tongue motion obtained are presently under investigation, some interesting observations already have been made. New instrumentation is presently being evaluated to implement this technique without the need for an intermediate photograph. In order to observe one's natural tongue motion, a critical task will involve developing a means to mount the ultrasonic probe so as not to interfere with or influence the patient's speech. Additionally, variable positioning or nonconstant pressure on the transducer will affect the final image.

Progress in FY82: In order to demonstrate the feasibility of the above-mentioned technique, the oral cavities of several normal subjects were scanned using a realtime ultrasonic body scanner, by placing the ultrasonic transducer two centimeters behind the mental symphysis of the patient's mandible. Each subject was asked to repeat specific phonemes while mouth images were continuously recorded on a videotape recorder. Using the recorder's freeze-frame capability in conjunction with a multi-image x-ray formatter, the desired images were copied onto negative film. The negatives were developed into positive prints. By placing the resultant prints on a graphic tablet connected by telephone to a DECsystem-10 computer, the polar coordinates of anatomical areas of interest, namely, the tongue surface and the genioglossus muscle, could be readily determined. The digitization technique was repeated by several observers in order to statistically determine the accuracy and reliability of both the ultrasonic imaging and digitization techniques. Preliminary observations were made regarding tongue motion for vocalizing particular phonemes.

Since the Rehabilitation Medicine Department wishes to outfit its new speech lab with an ultrasonic

imaging and analysis capability, various equipment and methods are being evaluated for integration into a tongue analysis system.

Proposed Course: The required system hardware will be ordered early in FY83. The development of methodology and software for analysis of tongue images will continue. A means for placing an ultrasonic transducer with constant position and pressure two centimeters behind the mental symphysis of the patient's mandible will be further investigated and developed. Once all the system hardware is obtained, the various components will be interfaced and the necessary control and processing software will be written. Normal volunteers will then be scanned in order to obtain baseline values of tongue motion. Shortly thereafter, patients with speech problems will be observed as well. In the future, we also plan to use this system to study swallowing defects.

Anesthesia Computer System

This project involves evaluating improved instrumentation techniques and identifying and investigating ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring and automated recordkeeping in the operating room.

Background and Objectives: While computers and automation have been used in intensive care settings for some time, little previous work has been reported on their application in operating rooms. Two areas of potential benefit with an anesthesia computer have been identified.

1. Adjunctive monitoring, i.e., using the computer for monitoring and display of patient parameters. The main goals are a unified, easy-to-read display; limit detection and trend analysis of the parameters; and archiving of the measurements for later use in research or anesthesia mishap analysis.

2. Automated recordkeeping, in which the computer would not only record the results of monitoring, but also would make provision for a record of drug administration, for free text notes by the anesthesiologist, and for producing a printed record suitable for inclusion in the patient's record. An advantage of such a system is that it will allow the anesthesiologist to devote more time to the patient by simplifying the tasks of observing and recording measurements.

Progress in FY82: Most effort this year has been expended on developing a project plan for future work.

Proposed Course: The project plan will be completed, needed resources will be sought, and

ANTHROPOMETER (GENERAL INFORMATION EXCHANGE) PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE OFFICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00093-01 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (DO NOT use this space) Anesthesia Computer System		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: P. S. Plexico Chief, Project Development Section CSL, DCRT OTHER: D. Lees, M.D. Chief, Anesthesia Service CC		
COOPERATING UNITS (if any) Anesthesia Service, CC		
LABORATORY Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANPOWER	PROFESSIONALS	OTHERS
0.2	0.2	
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (d) MINORS <input type="checkbox"/> (e) INTERVIEW SUMMARY OF WORK (200 words or less - underline keywords) This project involves evaluating improved instrumentation techniques and identifying and investigating ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring and automated recordkeeping in the operating room.		

PHS-6040
(Rev. 2-81)

efforts to accomplish the project plan will proceed to the extent that resources become available. The most likely scenario is the development of a 'demonstration' operating room to test the hypotheses that adjunctive monitoring and automated recordkeeping are advantageous.

Medical Information Technology Project

This project involves the application of microprocessor technology and improved man-machine interface methods to permit physicians and their associates to more directly communicate with computer record systems. A pilot study involving medical transactions input directly by practicing physicians is underway. The goal is to develop better ways to automate the essential physician contribution to the health care record that is used in both research and patient care.

Background and Objectives: The use of computers in medical and hospital practice is increasing as the cost of systems is decreasing due to technological innovation. However, few physicians are comfortable with current machine interfaces. With this in mind, we are investigating devices and methods that provide a more capable, attractive interface while maintaining an acceptable level of flexibility and efficiency. The ultimate aim is to increase physician productivity in patient diagnosis and treatment and to increase patient understanding of disease processes and management plans.

Methods: Much of the clinical software is table-driven to allow the physician to add and modify the data bases. This approach also provides a convenient means of adapting the programs to other clinical care and research environments. Both the clinical data base and processing software are being developed and tested on the CSL time-shared computer system. Finished programs, ready for use in patient care, are then transferred to a compatible microcomputer system situated in the physician's office.

Progress in FY82: In collaboration with a practicing dermatologist, we are field testing an ambulatory patient care transaction system. This system allows the physician to input, store, retrieve, and disseminate patient data needed by various members of the health care team as well as by the patient. The immediate data processing focus includes machine generation of patient information and treatment schedules, pharmacy prescriptions, medical and surgical procedure reports, laboratory test orders, and referral letters to other doctors.

Disease-specific and problem-specific protocols are used to lead the user through a restricted tree-structured hierarchy of relevant diagnoses,

ANTHROPOMETER (GENERAL INFORMATION EXCHANGE) PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE OFFICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00065-03 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (DO NOT use this space) Medical Information Technology Project		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: S.L. Allen Medical Research Analyst CSL, DCRT OTHERS: D. C. Songco Electronics Engineer CSL, DCRT C. S. Brown Consulting Dermatologist P. S. Plexico Chief, Project Development Sec. CSL, DCRT A. W. Pratt Director		
COOPERATING UNITS (if any) None		
LABORATORY Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANPOWER	PROFESSIONALS	OTHERS
1.0	1.0	
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (d) MINORS <input type="checkbox"/> (e) INTERVIEW SUMMARY OF WORK (200 words or less - underline keywords) This project involves the application of microprocessor technology and improved man-machine interface methods to permit physicians and their associates to more directly communicate with computer record systems. A pilot study involving medical transactions input directly by practicing physicians is underway. The goal is to develop better ways to automate the essential physician contribution to the health care record that is used in both research and patient care.		

PHS-6040
(Rev. 2-81)

treatments, drugs, tests, and procedures. Where appropriate, protocols are modified by such factors as patient age, sex, weight, disease stage, and therapeutic response specified by the physician. When all workups and treatments are indicated, the computer then produces hardcopy treatment plans for the patient, record summaries for the doctor, prescriptions for the pharmacist, and test requests for specified laboratories.

Proposed Course: Selected physician-operated modules will be tested to support critical diagnostic and therapeutic functions in ambulatory care. Programming logic to support isolated patient encounters also will be expanded to handle followup visits. The conventional CRT and keyboard terminal employed now will be replaced with faster I/O devices that are tailored to this medical application. For example, we plan to use graphic input to facilitate the capture of anatomic disease descriptions and keyboard substitutes to speed menu item selection.

Molecular Graphics and Sequence Analysis

The sequence of some regular proteins, together with other structural information such as data from x-ray diffraction, fiber diffraction, electron microscopy, and spectroscopic analysis can be used to evaluate models of the protein structure. Four such analyses are studies of collagen (with NIDR), keratin (with NIADDK and NCI), myosin (with Brookhaven), and streptococcal M proteins (with Rockefeller).

The crystallographic structure of type I collagen fibrils had previously contained some controversial assumptions. A new model has been proposed this year that seems to resolve these difficulties and encompasses all of the experimental evidence into one structurally simple model.

As the sequence of keratin cyanogen bromide fragments becomes available, an analysis of the sequence is proceeding by studying the periodicities in the sequence, and by predicting conformational properties of the specific amino acids in local regions of the chain. It is anticipated that the experimental results may be able to clearly specify if any of the proposed two or three models are correct.

Analysis of myosin and streptococcal M proteins is continuing as sequences become available. This project is presently capable of easily evaluating new sequences for periodicities or regularities.

Background and Objectives: While it would be somewhat idealistic to attempt to predict the structure of a globular or irregular protein, it is currently possible to convincingly model and predict

the structure of regular (helical) proteins. With the current knowledge of the structure of the collagen helix, synthetic protein analogues of collagen, tropomyosin, and other regular proteins, one can extend this technology to new proteins as the sequence is experimentally determined if there are known points of similarity.

Significance to Biomedical Research: Many proteins do not form three-dimensional crystalline solids whose structures can be analyzed by classical x-ray diffraction. However, if these proteins are regular, comparison and analogy with related proteins can be used to model the unknown structures in order to understand the structure and functioning of the proteins. In addition, one can use computer models to analyze two or more possible candidates and determine the most likely protein structure.

Progress in FY82: A new model of collagen has been proposed that reconciles previously diverse data from a variety of experimental sources. A new analysis has begun that will use the sequence of keratin filaments to compare the structure to proposed models and to other proteins whose structure has been well characterized.

Methods Employed: Standard Fourier methods have been used to analyze the sequences and to cross-correlate sequences. These sequence regularities are usually correlated with structural features, such as the collagen triple helix, the alpha helix, or the tropomyosin double-stranded alpha helix. In addition, software was written to model the collagen helix and double-stranded alpha helices on the Evans and Sutherland Picture System. This unique hardware allows three-dimensional analysis of proposed structures, both using traditional wire models, and by using CPK 'ball' models in three dimensions, where the size of the ball is related to the size of the individual amino acid, and the color of the ball is related to the function of the amino acid.

Proposed Course: As new sequences of regular (helical) proteins become available, it is relatively easy to model these sequences and describe their structures both graphically and quantitatively.

Publications:

Trus, B. L., and Elzinga, M.: Computer Modeling of A 17,000 Dalton Fragment of Myosin. In Balaban, M., Sussman, J. L., Traub, W., and Yonath, A. (Eds.): *Structural Aspects of Recognition and Assembly in Biological Macromolecules*, Rehovot, Israel (in press).

Piez, K. A., and Trus, B. L.: A new model for packing of type-I collagen molecules in the native fibril. *Bioscience Reports* 1:801-810, 1981.

BIOCHEMISTRY (SCIENCE INFORMATION EXCHANGE) PROJECT NUMBER (ON WFO AND THIS FORM) PERIOD COVERED TITLE OF PROJECT (80 characters or less) Molecular Graphics and Sequence Analysis	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT Z01 CT00090-D1 CSL	PROJECT NUMBER Z01 CT00090-D1 CSL
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: R. L. Trus Research Chemist CSL, DCRT OTHERS: A. C. Steven Visiting Scientist LRP, NIADDK P. M. Steinert Visiting Scientist DR, NCI R. L. Jernigan Theoretical Physical Chemist LTR, DCRO M. Elzinga Brookhaven National Laboratory NCI B. N. Manjula The Rockefeller University V. A. Fischetti The Rockefeller University		
COOPERATING UNITS (if any) LRP, NIADDK; DR, NCI; LTR, NCI; Biology Dept., RNL; Microbiology, Rockefeller University		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANIFEST PROFESSIONAL		
CHECK APPROPRIATE BOXES <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NUCLEAR		
<input type="checkbox"/> (a) MINDS <input type="checkbox"/> (a) INTERVIEWS SUMMARY OF WORK (200 words or less - underline keywords) The sequence of some regular proteins, together with other structural information such as data from x-ray diffraction, fiber diffraction, electron microscopy, and spectroscopic analysis can be used to evaluate models of the protein structure. Four such analyses are studies of collagen (with NIDR), keratin (with NIADDK and NCI), myosin (with Brookhaven), and streptococcal M proteins (with Rockefeller).		
PHS-640 (Rev. 2-82)		

Computer Analysis of Gel Electrophoresis

This project was designed to allow NIH scientists to easily and accurately quantitate one- and two-dimensional gels. Quantitative comparisons of two gels is semi-automatic, and one project has used methods developed here to separate the results of double-labeled radiography of protein gels using color negative film and appropriate filters. This is possible because 3H and spillover of 14C are recorded in the blue sensitive layer of the film while 14C alone is recorded in the green or red sensitive layer. This method was used to analyze the effect of growth rate and medium composition on the relative levels of individual proteins in a pathogenic strain of *Escherichia coli*.

Background and Objectives: The primary objective of this project has been to develop experimental techniques and computer software to easily and automatically quantitate two-dimensional gels. In addition, analysis of one-dimensional gels is equally accurate and feasible. Initially only Coomassie blue stained gels were analyzed, but currently autoradiographs are equally amenable to processing.

Significance to Biomedical Research: Use of gel electrophoresis and autoradiographs is commonplace in chemical, biochemical, and biomedical research. However, the quantitation of these gels is difficult. We have developed systems that accurately and easily provide this quantitation to the scientist. A number of laboratories outside of NIH have requested our software for private use.

Progress in FY82: This project has produced many useful results to a number of scientists at NIH. As new gels require analysis, further fine tuning of the methods will continue to improve the product. In addition, we have used the methods to analyze color negative film (rephotographed through appropriate color filters) so as to analyze the growth rates and medium composition on the relative levels of individual proteins in a pathogenic strain of *Escherichia coli*. These results are being submitted for publication.

BIOCHEMISTRY (SCIENCE INFORMATION EXCHANGE) PROJECT NUMBER (ON WFO AND THIS FORM) PERIOD COVERED TITLE OF PROJECT (80 characters or less) Computer Analysis of Gel Electrophoresis	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT Z01 CT00090-D2 CSL	PROJECT NUMBER Z01 CT00090-D2 CSL
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: R. L. Trus Research Chemist CSL, DCRT OTHERS: R. Goldman Staff Fellow LRP, NIADDK V. Nivodnen Staff Fellow CE, NIADDK J. E. Hall Director NIADDK R. Felsted Research Chemist BCRP, NCI Baltimore Cancer Research Program		
COOPERATING UNITS (if any) LRP, NIADDK; CE, NIADDK; BCRP, NCI		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANIFEST PROFESSIONAL		
CHECK APPROPRIATE BOXES <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NUCLEAR		
<input type="checkbox"/> (a) MINDS <input type="checkbox"/> (a) INTERVIEWS SUMMARY OF WORK (200 words or less - underline keywords) This project was designed to allow NIH scientists to easily and accurately quantitate one- and two-dimensional gels. Quantitative comparisons of two gels is semi-automatic, and one project has used methods developed here to separate the results of double-labeled radiography of protein gels using color negative film and appropriate filters. This is possible because 3H and spillover of 14C are recorded in the blue sensitive layer of the film while 14C alone is recorded in the green or red sensitive layer. This method was used to analyze the effect of growth rate and medium composition on the relative levels of individual proteins in a pathogenic strain of <i>Escherichia coli</i> .		
PHS-640 (Rev. 2-82)		

Methods Employed: Gels were rephotographed onto Ektapan 4162 black and white film. Color films were photographed through appropriate color filters. The black and white negative was scanned on the Perkin-Elmer microdensitometer and stored on tape for later processing. A computer program CINT was used to analyze the two-dimensional gels, and another program OVERLP was used to correlate two gels when necessary or desired. PIC was used in the one-dimensional analyses.

Proposed Course: Computer software is being expanded to provide for better matching of two gels. All software is essentially machine independent so as to be transferred to the newly-acquired image processing laboratory. Additional options are being added to the software so as to provide additional flexibility to the research scientist.

Publication:

Nikodem, V. M., Trus, B. L., and Rall, J. E.: Two-dimensional gel analysis of rat liver nuclear proteins after thyroidectomy and thyroid hormone treatment. *Proceedings of the National Academy of Science* 78:4411-4415, 1981.

Morphometric Analysis of Normal and Neoplastic Tissue Cultures

This project was designed to study the morphometric differences between normal and tumorigenic fibroblastic cell lines. Initially, human, rat, and mouse cell lines were selected for analysis. The cells were photographed from living cultures without staining or fixing. The types of criterion being used by the computer to aid in differentiating between normal and tumorigenic cells include nucleus and nucleolus size and shape, and chromatin texture and clumping.

Background and Objectives: This project, which was begun this year, uses standard techniques of image processing as applied to these low contrast unstained specimens as well as techniques developed at NIH. We hope to demonstrate that it is possible and practical to differentiate between normal and tumorigenic cells in a nondestructive manner. We are using many of the same criterion used by the pathologist in differentiating stained and fixed sections.

Significance to Biomedical Research: We hope to demonstrate that this nondestructive method can be used with confidence to determine if a culture is normal. This method would be important for studies of carcinogenesis in cultures.

Progress in FY82: Software was developed to perform a pilot study on three types of cultures. Preliminary results suggest that it may be possible to determine statistical differences between normal and abnormal cells.

Methods Employed: Cell cultures were photographed through a light microscope onto 35 mm black and white film. The film was digitized by a Perkin-Elmer 1010G microdensitometer with a 50 microns squared aperture. Images were viewed on a video frame buffer, and interactively processed. Results are stored in log files for each sample, and files are pooled for each type of culture yielding better statistics. The mouse and rat cultures underwent spontaneous neoplastic transformation, while the human fibroblast line was exposed to chemical carcinogens to generate the tumorigenic line.

Proposed Course: After the analysis of the three pilot studies, we expect to continue analysis of additional cell lines, and are considering nonlethal staining techniques.

ORIGINATOR (AGENCY, DIVISION, OFFICE) PROJECT NUMBER (DO NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH NATIONAL CANCER INSTITUTE INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER 201 CT00091-01 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (10 characters or less) Morphometric Analysis of Normal and Neoplastic Tissue Cultures		
NAMES, LAST-NAME AND INITIALS, AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: R. L. Trus Research Chemist CSL, DCRT OTHERS: K. K. Sanford Chief, In Vitro Carcinogenesis Section LCMR, NCI G. Jones Microbiologist LCMR, NCI M. Weedon Laboratory Technician LCMR, NCI		
COOPERATING UNITS (if any) LB, NCI		
LABORATORY Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MATERIALS	PROFESSIONAL	OTHER
CHECK APPROPRIATE BOXES <input type="checkbox"/> (a) HUMAN SUBJECTS <input checked="" type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input checked="" type="checkbox"/> (d) MAMMARY <input type="checkbox"/> (e) INTERVIEW		
SUMMARY OF WORK (100 words or less - underline keywords) This project was designed to study the morphometric differences between normal and tumorigenic fibroblastic cell lines. Initially, human, rat, and mouse cell lines were selected for analysis. The cells were photographed from living cultures without staining or fixing. The types of criterion being used by the computer to aid in differentiating between normal and tumorigenic cells include nucleus and nucleolus size and shape, and chromatin texture and clumping.		

PH-0040
(Rev. 2-81)

Virus Structure As Determined by Image Processing of Electron Micrographs

A new virus structure, that of bacteriophage T7, has been determined by image processing of electron micrographs. We analyzed T7 polycapsid tubes because these structures are more amenable to image processing. Optical diffraction revealed that the polycapsids were based on cylindrical foldings of a hexagonal lattice with a spacing of 12.6 nm, which is similar to the lattice constant for other complex icosahedral phage capsids defined to date. However, the details of the T7 capsomer differ from the other results.

Background and Objectives: Viruses are significantly smaller than bacteria, and as a result are not seen in a light microscope. Information about their structure usually comes from electron microscopy, which is limited by resolution, low contrast, and noise. If staining is used, then the resolution is limited by the size of the stain, and often has noise as a result of uneven staining. However, because virus structures are generally periodic, they are a perfect candidate for image processing.

Virus shells are composed of one or a few proteins that form simple repetitive geometric forms. The forms or containers can be, for example, cylinders, icosahedra, or spheres. There are classes of structures, and knowledge of the fine structure of one coat protein can be used to understand the structures of other similar viruses in the class. It is our primary objective to add to the pool of information, and to be able to use this information to increase our understanding about how virus structure relates to function and activity. This project was described under project number Z01 CT00082-01 CSL in FY81.

Progress in FY82: The results of a study of a virus previously determined by us, beet necrotic yellow vein virus, were published. In addition, the results of the structural determination of the T7 virus were presented at two meetings, and are being submitted for publication. These results are especially significant because another virus (polyoma), which has significant similarities to T7, was recently reported to have significantly differing geometry.

Significance to Biomedical Research: This project should be considered as basic research whose aim is to increase our understanding of the structure and functions of viruses in general, as well as subclasses of viruses similar to those studied to date.

Methods Employed: The micrographs were taken with a Philips EM400T microscope, and the best negatives were preselected by optical diffraction.

Negatives were digitized on a Perkin-Elmer 1010G microdensitometer and analyzed by means of the PIC computer system. Results were photowritten on the Perkin-Elmer microdensitometer. Typical processing of the images consisted of Fourier filtering of up to 50 unit cells and symmetrization of the results as needed.

Proposed Course: We anticipate evaluating other viruses for suitability for examination with these methods, and continuing with this project to determine the structure of various classes of viruses.

Publications:

- Steven, A. C., Trus, B. L., Putz, C., and Wurtz, M.: The Molecular Organization of Beet Necrotic Yellow Vein Virus. *Virology* 113:428-438, 1981.
- Steven, A. C., Serwer, P., and Trus, B. L.: Molecular Packing in Bacteriophage T7 Capsid Visualized at 2.5 nm Resolution in Computer Processed Electron Micrographs. Eighth Biennial Conference on Bacteriophage Assembly, Fall Creek Falls Park, Tennessee, May 9-14, 1982.
- Trus, B. L., Serwer, P., and Steven, A. C.: Capsid Fine Structure of Bacteriophage T7 Determined by Image Processing of Electron Micrographs. Tenth International Congress on Electron Microscopy, Hamburg, Germany, August 17-24, 1982.

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (UP TO 40 CHARACTERS)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF HEALTH	PROJECT NUMBER Z01 CT00082-01 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (50 characters or less) Virus Structure As Determined by Image Processing of Electron Micrographs		
NAME(S), LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATOR(S) AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: R. L. Trus Research Chemist CSL, DCRT OTHERS: A. C. Steven Visiting Scientist LPR, NEADOK P. Serwer The University of Texas Health Sci. Ctr.		
COORDINATING UNIT (1 = a, 2 = b) LPR, NEADOK; The University of Texas Health Science Center		
LABORATORY Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANHOURS 4 PROFESSIONAL 4 OTHER		
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) ANIMAL <input type="checkbox"/> (d) MINORS <input type="checkbox"/> (e) INTERVIEWING SUMMARY OF WORK (200 words or less - underline keywords) A new virus structure, that of bacteriophage T7, has been determined by image processing of electron micrographs. We analyzed T7 polycapsid tubes because these structures are more amenable to image processing. Optical diffraction revealed that the polycapsids were based on cylindrical foldings of a hexagonal lattice with a spacing of 12.6 nm, which is similar to the lattice constant for other complex icosahedral phage capsids defined to date. However, the details of details of the T7 capsomer differ from the other results.		

PH-4080
(Rev. 2-81)

Image Processing of Electron Micrographs

This project was designed to facilitate structure determination from electron microscopy by providing suitable software, hardware, and scientific expertise to allow other scientists, primarily at NIH, to use image processing and computer reconstruction to determine or understand a specimen's structure.

Two new applications that began this year are analysis and identification of small particles by electron beam excited x-ray microanalysis as applied to aqueous suspensions of vertebrate retinal rod cells and the analysis of the microtrabecular lattice and the cytoskeleton to determine volume, surface area, and the diffusion of molecules.

A study of densitometer techniques was completed and published. Studies continued from FY81 include analysis of keratin, membrane structure, and muscle structure.

Background and Objectives: The objective of this project is to develop a general-purpose software package for the analysis of electron micrographs. In addition, the computer analysis requires optimal utilization of the available hardware and the availability of a research scientist capable of providing logistical support. Techniques and software developed in this project have been used independently of this project both at NIH and at laboratories outside NIH.

Significance to Biomedical Research: Computer analysis of electron micrographs is still a relatively recent addition to the tools available to scientists for structural analysis. Few laboratories have the combined software and hardware capability to perform the image processing and image reconstruction available at NIH. These techniques are especially powerful when applied to two-dimensional crystalline structures. In addition, we can correlate and align similar particles that are not crystalline, and correct for a number of artifacts and experimental problems.

Progress in FY82: This project has had some growth in software, but primarily has grown in the utilization of programs and the PIC system. It is feasible for an NIH scientist to bring in a problem and obtain preliminary results in a relatively short period of time. Then a decision is made to expand the preliminary study into a project, or to use the results that were obtained.

One study, in collaboration with NIADDK, used the computer to analyze digital information to analyze small particles by electron beam excited x-ray microanalysis for particles in aqueous suspension. This novel approach was applied to the isolated outer segments of vertebrate retinal rod cells and was used to study the distribution of K, Os, P, and ⁴⁵Ca in unstable objects.

Another study, in collaboration with the Physical Sciences Laboratory, DCRT, examined the microtrabecular lattice and the cytoskeleton. Images were digitized and analyzed for the fraction of interlinked slender strands versus the amount of open spaces.

Proposed Course: This project will continue software development as needed and will be converted to use the new image processing facility as it becomes available. In addition, new biological structures that become available for analysis will be examined.

Publications:

- McGee, P. A., Trus, B. L., and Steven, A. C.: Techniques to Evaluate the performance of Scanning Microdensitometers in the Digitization of Electron Micrographs. *Micron* (in press).
- Trus, B. L., and Steven, A. C.: Computer Processing of Electron Micrographs of Periodic Biological Specimens. Washington Society of Electron Microscopy Annual Picture Meeting, Uniformed Services, University of the Health Sciences, Bethesda, MD, May 6, 1982.
- Gershon, N. D., Porter, K. R., and Trus, B. L.: The Microtrabecular Lattice and the Cytoskeleton. Their Volume, Surface Area and the Diffusion of Molecules Through It. Aharon Katzir-Katchalsky Symposium on Biological Structure and Coupled Flows, Rehovot, Israel, June 6-11, 1982.
- Hagins, W. A., Foster, M. C., George, J. G., and Trus, B. L.: Combined X-ray Microanalysis and Radioautography of Diffusible Elements in Aqueous Suspensions of Cells and Cell Fragments. Proceedings of Microbeam Analysis Society, August 1982.
- Trus, B., and Steven, A.: Digital Image Processing of Electron Micrographs--The PIC System. *Journal of Ultramicroscopy* 6: 383-386, 1981.

INTERDISCIPLINARY SCIENCE INFORMATION TECHNOLOGY PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CD00002-D2 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (in brackets or lines) Image Processing of Electron Micrographs		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: B. L. Trus Research Chemist CSL, DCRT OTHERS: A. C. Steven Visiting Scientist LCB, NIAADK M. A. Hagins Chief, Section on Membrane Biophysics LCB, NIAADK M. C. Foster LPA Appointee/Guest Worker LCB, NIAADK J. G. George Laboratory Technician LCB, NIAADK N. D. Gershon Senior Staff Fellow PSL, DCRT K. Porter University of Colorado and Fogarty Scholar		
COOPERATING UNITS (if any) LCB, NIAADK; LCB, NIAADK; PSL, DCRT; University of Colorado		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL WORKLOAD 2 PROFESSIONAL 2 OTHER		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) BOTH		
<input checked="" type="checkbox"/> (a) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS SUMMARY OF WORK (Do NOT write or less - underline beyond) This project was designed to facilitate structure determination from electron microscopy by providing suitable software, hardware, and scientific expertise to allow other scientists, primarily at NIH, to use image processing and computer reconstruction to determine or understand a specimen's structure. Two new applications that began this year are the analysis and identification of small particles by electron beam excited x-ray microanalysis as applied to aqueous suspensions of vertebrate retinal rod cells and the analysis of the microtrabecular lattice and the cytoskeleton to determine volume, surface area, and the diffusion of molecules.		

PHS-0040
(Rev. 7-82)

INTERDISCIPLINARY SCIENCE INFORMATION TECHNOLOGY PROJECT NUMBER (Do NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CD00045-01 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (in brackets or lines) Potentiometric Titration Controller		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: D. C. Songco Electronics Engineer CSL, DCRT OTHERS: R. W. Hendler Chief, MES LCB, IR, NHLRI P. Reddy Visiting Fellow LCB, IR, NHLRI R. Shrago Mathematician LAS, DCRT		
COOPERATING UNITS (if any) LCB, IR, NHLRI		
LAB/BRANCH Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL WORKLOAD 1 PROFESSIONAL 1 OTHER		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) BOTH		
<input checked="" type="checkbox"/> (a) MINORS <input checked="" type="checkbox"/> (a2) INTERVIEWS SUMMARY OF WORK (Do NOT write or less - underline beyond) A Potentiometric Titration Controller was developed to study the electron transport chain at the cell level. The details of this system have been reported in previous years. The original configuration was used to study the E. coli bacteria system. This year a new system incorporating a rapid scan spectrophotometer (RSS) is being used to study mammalian cells.		

PHS-0040
(Rev. 7-82)

Potentiometric Titration Controller

A Potentiometric Titration Controller was developed to study the electron transport chain at the cell level. The details of this system have been reported in previous years. The original configuration was used to study the E. coli bacteria system. This year a new system incorporating a rapid scan spectrophotometer (RSS) is being used to study mammalian cells.

Background and Objectives: The exact nature of the respiratory chain in the mitochondria of mammalian cells is still not known. The carriers are various iron-containing molecules that have different affinities (and corresponding voltages) by which they hold electrons. The amount of energy liberated by passage of an electron from one carrier to another can be determined by the difference in redox potentials of these carriers. The redox potential is the voltage at which the carrier is equally reduced and oxidized and it can be determined by a Nernst relationship.

The original Potentiometric Titration Controller could fix solution potential using electric currents under program control. The amounts of oxidized and reduced transport carriers were determined by calculations based on voltages obtained from the spectrophotometer corresponding to optical transmittance and wavelength. A wavelength scan motor was driven under computer control to change the wavelength and obtain complete spectra.

Progress in FY82: The Potentiometric Titration Controller has been greatly enhanced with the addition of a Rapid Scan spectrophotometer (RSS) in place of the original device. As before, the solution potential is fixed by using electric currents and the amounts of oxidized and reduced electron transport carriers are determined using spectral data. Now, however, complete optical spectra can be taken in milliseconds instead of the 20 to 30 seconds required by the earlier system. Instead of controlling a wavelength drive motor to acquire spectra, entire scans are initiated under microcomputer control. Complete scan data is stored in an internal memory buffer of the RSS. Either single scans or up to 64 rapid successive scans can be taken and stored in the buffer. Data is then transferred to the controller via a 9600 baud serial link and recorded on disk. As before, selected data is then transferred via modem to the DECsystem-10 for further analysis and graphics.

Proposed Course: The earlier Potentiometric Titration Controller was used to study the electron transport chain of a bacterial system, *E. coli*. A similar approach using the new RSS will now be used to extend these studies to the chain in mammalian mitochondria. In addition, the new system will enable us to study other important kinetic features of respiratory systems not possible with the original system.

Metabolic Energy Measurements

A microcomputer-based instrument has been developed to study cellular energy transduction phenomena. Specially designed electrodes have been constructed and interfaced to the microcomputer to calculate membrane potential and protonmotive force. Derived parameters are recorded in realtime on a multipen plotter via D/A converters. The user can observe all parameters as he perturbs alterations to the medium in which the respiring and energy transducing systems are suspended.

Background and Objectives: Cellular energy is derived from the oxidation of substrates. Electrons removed from these substrates are passed through a chain of respiratory carriers—eventually, oxygen. During the process, energy is stored in the form of a gradient of protons across the cell or mitochondrial membrane. The difference in the number of protons inside the cell and outside the cell results in an electrochemical potential or protonmotive force. This electrochemical potential has two components, an electrical potential across the membrane, and a chemical potential characterized by a difference in pH. These quantities are very difficult to measure and current techniques are cumbersome and time-consuming.

Progress in FY82: In FY80 and FY81 we developed a microcomputer-based system that is capable of realtime monitoring of these components. In FY82 specific electrodes have been designed and constructed that respond to changes in electrical potential and to changes in pH. The voltage signals from these electrodes are amplified and sent to the microcomputer via an analog-to-digital converter. The computer stores the signals after digitally filtering out noise and correcting for the nonlinearity of the electrode transfer functions. It then computes the electrical potential and the difference in pH from the measured electrode voltages, and from these determines protonmotive force.

The microcomputer also monitors signals from a pH electrode and an oxygen-measuring electrode. The computer program corrects for relaxation time delays in electrode responses and filters out noise. The oxygen uptake rate of the cellular material is calculated as are the proton extrusion rate and the proton-to-oxygen ratio. All derived parameters are calculated in realtime and are output via D/A converters to a multipen plotter. In this manner the user can observe all quantified parameters in parallel as he alters the medium in which the respiring and energy-transducing system is suspended.

Proposed Course: Hardware and software development are now complete and all programs reside in ROM and therefore do not require downloading as before. The emphasis next year will be on acquiring and analyzing data. New hardware and software will be developed as the need arises.

NATIONAL SCIENCE FOUNDATION EXCHANGE PROJECT NUMBER (DO NOT WRITE IN THIS SPACE)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00062-03 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982			
TITLE OF PROJECT (40 characters or less) Metabolic Energy Measurements			
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
PI: D. C. Sengco		Electronics Engineer CSL, DCR	
OTHERS: R. W. Wendler D. H. Setty R. Shrago W. Prieuf		Chief, MES Visiting Associate Mathematician Chief, EES	
		LCB, IR, NHLBI LCB, IR, NHLBI LAS, DCR BCTR, DRS	
COOPERATING UNITS (4 v.v.) LCB, IR, NHLBI			
LABORATORY Computer Systems Laboratory			
SECTION Project Development Section			
INSTITUTE AND LOCATION DCR, NIH, Bethesda, MD 20205			
TOTAL MANPOWER: 2		PROFESSIONAL: 2	
CHECK APPROPRIATE BOX(ES)			
<input type="checkbox"/> (a) HUMAN SUBJECTS		<input type="checkbox"/> (b) HUMAN TISSUES	
<input type="checkbox"/> (c) MINDS		<input type="checkbox"/> (d) INTERVIEW	
SUMMARY OF WORK (200 words or less - underline keywords)			
A microcomputer-based instrument has been developed to study cellular energy transduction phenomena. Specially designed electrodes have been constructed and interfaced to the microcomputer to calculate membrane potential and protonmotive force. Derived parameters are recorded in realtime on a multipen plotter via D/A converters. The user can observe all parameters as he perturbs alterations to the medium in which the respiring and energy transducing systems are suspended.			

FD-500
(Rev. 2-81)

Electron Microanalysis Facility

CSL is collaborating with BEIB, DRS, in developing an automated electron microanalysis facility consisting of two electron microscopes interfaced to a computer system. The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL is designing and implementing the computer system, which will acquire and display the spectra and images produced by Electron Energy Loss Spectrometry, Energy-Dispersive x-ray Spectrometry, and Wavelength Dispersive x-ray Spectrometry. (See also: Z01 RS10058-04 and Z01 RS10059-04.)

Background and Objectives: The Computer Systems Laboratory is designing and implementing a computer system as part of the BEIB Electron Beam Imaging and Microspectroscopy Facility. The facility consists of two electron microscopes and will be used for research into the elemental composition of biological specimens and for developing new techniques in electron microscopy.

One of the electron microscopes is a Hitachi H-700H 200 keV Scanning Transmission Electron Microscope (STEM) equipped with:

- a lithium-drifted silicon (Si(Li)) detector connected to a Kevex 7000 Analytical Spectrometer for performing Energy-Dispersive x-ray Spectrometry (EDS)
- an electron spectrometer for performing Electron Energy Loss Spectrometry (EELS)
- detectors for bright and dark field electron current signals.

The other electron microscope is a Cameca 50 keV Electron Microprobe equipped with:

- a Si(Li) detector for performing EDS
- three Wavelength Dispersive x-ray (WDS) spectrometers
- detectors for bright and dark field electron current signals.

A PDP-11/60 computer system is being interfaced to both microscopes to perform the following functions:

- control electron beam position, stage position, and the various detectors
- acquire spectral and image data from all detectors
- process and display the spectral and image data
- monitor and display a wide variety of 'housekeeping' parameters, including: lens currents, lens temperatures, beam current, beam

energy, pump temperatures, coolant flow, vacuum pressures, water leak detectors, power supply voltages, room temperature, and room humidity.

Progress in FY82: CSL's software efforts this year have been concentrated on these aspects of data acquisition from the STEM:

- improvement of EEL spectral data acquisition and display
- implementation of EEL and EDS image acquisition and display
- implementation of fast electron current signal acquisition and display
- retrieval of empirical x-ray spectral data
- improvement of the Kevex 7000 and housekeeping data acquisition software
- development of a user interface.

EELS data acquisition and control of the STEM beam position is done by a satellite processor connected to the PDP-11/60 by a high-speed link. Software has been written that allows the STEM operator to define areas of a specimen as targets for data acquisition and to collect EDS, EELS, and electron current signal data from the target areas.

Three data acquisition modes have been implemented:

- SPECTRUM mode produces a single x-ray and/or EEL spectrum from the target area.
- IMAGE mode produces any combination of EEL, EDS, or electron current signal images from the target area.
- FAST IMAGE mode produces only current signal images, but at high speed.

Software has been developed this fiscal year for display and scaling of EEL spectra using the Kevex 7000. Also, EEL, EDS, and electron current signal images can be displayed on the DeAnza ID5400 Display System, where zoom, scroll, and contrast/brightness enhancement can be performed.

Software to retrieve empirical x-ray spectral data produced by electron energy transitions within ionized atoms was completed. This software allows an operator or another programmer to specify an element and the transitions or absorption lines of interest using either Siegbahn or Shell-Pair notation. It then looks up the associated energies and relative peak intensities. Conversely, an energy range may be specified, in which case the transitions and absorption lines within that range are retrieved. The x-ray data base was assembled by BEIB from multiple sources, and contains over 3000 entries. The contractor validated this data by fitting each x-ray line series to a model based on Moseley's Law

and flagging for inspection any entry showing a large deviation from the theoretical value. The resulting data base is probably the most complete and accurate available in machine-readable form, and has been sent to over ten extramural requestors.

EDS data acquisition is done by the Kevex 7000, which is connected directly to the computer. Software has been developed to allow programs on the 11/60 to control the KEVEX 7000 and to save or restore spectra to or from disk files. During this fiscal year this software was improved to make it much more efficient and easier to use. It was also installed on a PDP-11/34 computer system connected to a JEOL JEM-100CX electron microscope for the Laboratory of Neuropathology and Neuroanatomical Sciences, NINCDS.

Housekeeping parameters are acquired by the computer by means of an Analogs AN5400 data acquisition subsystem. Software has been developed to acquire, monitor, and display the STEM beam energy, magnification, lens currents, pump temperatures, and coolant flow. Improved calibration parameter maintenance utilities also have been developed.

A menu selection scheme simplifies the operation of the data acquisition and display software. The menu selection software is completely table-driven so that it is easy to add new functions as they become available. Menu selection terminates with the display of a form for entering or modifying the parameters for the chosen function. Each form records the parameters last used and restores them as defaults the next time it is selected. This greatly simplifies operation, because most forms have dozens of parameters, few of which are changed with each use. Currently, forms for data acquisition and display functions, housekeeping parameter display, and specimen target definition can be activated through menu selection.

The microprobe was connected directly to the 11/60 with a serial interface, and BEIB has developed software for acquiring WDS data.

Proposed Course: Next year, we expect to:

- implement primitive image processing functions,
- enhance the data acquisition software, and
- automate reading of the STEM beam current.

Publications:

- Fiori, C. E., Gorlen, K. E., and Gibson, C.: Comments on the Computerization of an Analytical Electron Microscope. *Proceedings of the Thirty-Ninth Annual Meeting of the Electron Microscopy Society of America*, Baton Rouge, Claitor's Publishing Division, 1981, pp. 246-249.
- Fiori, C. E., Myklebust, R. L., and Gorlen, K. E.: Sequential Simplex: A Procedure for Resolving Spectral Interference in Energy Dispersive X-ray Spectrometry. *Energy Dispersive X-ray Spectrometry*, Gaithersburg, MD., National Bureau of Standards Special Publication 604, 1979, pp. 233-272.
- Fiori, C. E., Swyt, C. R., and Gorlen, K. E.: Application of the Top-Hat Digital Filter to a Nonlinear Spectral Unraveling Procedure in Energy-Dispersive X-ray Microanalysis. *Microbeam Analysis*. San Francisco, San Francisco Press, Inc., 1981, pp. 320-324.

BIOCHEMICAL SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT use this space)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES FOUR-25(10)G-1000 INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00601-03 CSL	
PERIOD COVERED OCTOBER 1, 1981 to September 30, 1982					
TITLE OF PROJECT (40 characters or less) Electron Microanalysis Facility					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, and TITLES of PRINCIPAL INVESTIGATORS and ALL OTHER PROFESSIONAL PERSONNEL WORKING ON THE PROJECT					
PI: K. E. Gorlen Electronics Engineer CSL, NCRT					
OTHERS: C. E. Fiori Physical Scientist REIR, DRS					
L. K. Barden Electronics Engineer CSL, NCRT					
J. S. Del Priore Mathematician CSL, NCRT					
P. S. Plexico Chief, Project Development CSL, NCRT					
C. C. Gibson REIR, DRS					
M. S. Eden REIR, DRS					
J. R. Ellis REIR, DRS					
G. R. Hook REIR, DRS					
R. R. Logman REIR, DRS					
C. R. Swyt REIR, DRS					
COOPERATING INSTIT: (if any) DRS; NHLBI; NIADDK; NIMH; NINCDS					
LAB/BRANCH Computer Systems Laboratory					
SECTION Project Development Section					
INSTITUTE AND LOCATION NCRT, NIH, Bethesda, MD. 20205					
TOTAL MANUSCRIPTS 3.0		PUBLICATIONS 3.0			
OTHER APPROVED MANUSCRIPTS <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) BEHAVIOR					
<input type="checkbox"/> (a) HUMAN <input type="checkbox"/> (a) INSECT <input type="checkbox"/> (a) PLANT					
SUMMARY OF WORK (200 words or less - underline keywords) CSL is collaborating with DRS/BEIR in developing an automated electron microanalysis facility consisting of two electron microscopes interfaced to a computer system. The facility will be used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL is designing and implementing the computer system, which will acquire and display the spectra and images produced by Electron Energy Loss Spectrometry, Energy-Dispersive X-ray Spectrometry, and Wavelength Dispersive X-ray Spectrometry.					
See also: Z01 R510058-04 Z01 R510059-04					

PHS-1040
(Rev. 2-74)

Molecular Interactions Laboratory Data System

This microcomputer (PDP 11/03) data system supervises the acquisition and processing of information from an analytical ultracentrifuge and a circular dichroic spectropolarimeter used in MDB, NHLBI, to investigate the interactions between human lipoprotein subunits.

Objectives and Methods: As a supplement to the ultracentrifuge data system, a microcomputer-based data acquisition and analysis system was developed for use with a Cary Model 61 CD spectropolarimeter. The system consists of a simple, flexible CD spectropolarimeter/microcomputer interface and an interactive data processing program system by which CD spectra may be acquired, averaged, subtracted, converted to mean residue ellipticities, printed, and stored for future use. Stored data may also be transferred conveniently to a large computer facility for semi-automatic conformation analysis. The system overcomes some of the difficulties encountered in attempting the visual interpretation of noisy CD spectral recordings and in providing additional data manipulation capabilities not easily realizable with manual methods.

The CD spectropolarimeter is interfaced with the microcomputer system via a special highly noise-immune interface scheme based on the conversion of the signals from the spectropolarimeter to pulse trains. These pulse trains are then transmitted via current loops to a CSL-designed timer/counter interface board in the microcomputer. The operating software consists of two programs that interact with the user through a standardized combination of menus and dynamically alterable displays. One program provides data acquisition, processing, output, and storage functions, while the other program provides all but acquisition and includes the capability to edit the operating parameters of a scan file stored on the diskette.

Progress in FY82: Considerable effort was spent this fiscal year in testing the system and in developing tools on the DECsystem-10 for the graphic display of spectra. The results of a study of system performance with very dilute solutions were presented at the 1982 FASEB meeting in New Orleans. The CD data system has proven to be efficient and easy to use; over 900 scans on several hundred samples have been processed in the past year. The time required to process a CD scan into mean residue ellipticities has been reduced from several hours to less than 30 seconds. In addition,

an arbitrary number of scans may be averaged, difference spectra may be generated quickly, and data at any stage of reduction may be stored for future retrieval and manipulation. With this system usable CD measurements have been obtained at protein concentrations below 1 microgram per milliliter.

Proposed Course: Plans for the future include modification of the ultracentrifuge interface to provide greater noise immunity and the addition of support for a digital plotter that has recently been added to the system.

Publication:

Tate, R., Schultz, A., and Osborne, J.: Computer-Assisted Analysis of apolipoprotein subunit interactions. *Federation Proceedings* 41: 874, 1982.

INSTITUTION: [] PROJECT NUMBER: [] TITLE: []	TITLE: [] PROJECT NUMBER: [] TITLE: []
PROJECT COVERED: []	
October 1, 1981 to September 30, 1982 (DATE OF PROJECT) (10 characters or less)	
Molecular Interactions Laboratory Data System	
NAME, LABORATORY AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT	
PI: R. L. Tate, Ph.D. OTHERS: J. C. Osborne, Ph.D. A. R. Schultz, Jr.	Computer Specialist Research Chemist Head, Processor Design Section CSL, NCRT MDB, NHLBI CSL, NCRT
COOPERATING UNIT: (1 + 2) MDB, NHLBI	
LAB/DEPT: [] SECTION: []	
INSTITUTION AND LOCATION: []	
NCRT, NIH, Bethesda, MD 20205	
TOTAL RESEARCH: [] (1) PROFESSIONALS [] (2) OTHER []	
CHECK APPROPRIATE BOXES: [] (1) HUMAN SUBJECTS [] (2) HUMAN TISSUES [] (3) ANIMAL []	
(1) (2) (3) (4) (5) (6) (7) (8) (9) (10) (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78) (79) (80) (81) (82) (83) (84) (85) (86) (87) (88) (89) (90) (91) (92) (93) (94) (95) (96) (97) (98) (99) (100)	
SUMMARY OF WORK (200 words or less - underline key words) This microcomputer (PDP 11/03) data system supervises the acquisition and processing of information from an analytical ultracentrifuge and a circular dichroic spectropolarimeter used in MDB, NHLBI, to investigate the interactions between human lipoprotein subunits. Current capabilities include acquisition, display, and preprocessing of data from the ultracentrifuge and transfer of preprocessed data files to the DECsystem-10 for further analysis under PLINK using predefined procedures. The system includes the ability to add, subtract, and average CD spectra and to transfer files to the PDP-10 for further analysis. The results of a study of system performance with very dilute solutions were presented at the 1982 FASEB meeting in New Orleans. Plans are now underway for modification of the ultracentrifuge interface to provide greater noise immunity and for the addition of a digital plotter to the system.	
(1) (2) (3) (4) (5) (6) (7) (8) (9) (10) (11) (12) (13) (14) (15) (16) (17) (18) (19) (20) (21) (22) (23) (24) (25) (26) (27) (28) (29) (30) (31) (32) (33) (34) (35) (36) (37) (38) (39) (40) (41) (42) (43) (44) (45) (46) (47) (48) (49) (50) (51) (52) (53) (54) (55) (56) (57) (58) (59) (60) (61) (62) (63) (64) (65) (66) (67) (68) (69) (70) (71) (72) (73) (74) (75) (76) (77) (78) (79) (80) (81) (82) (83) (84) (85) (86) (87) (88) (89) (90) (91) (92) (93) (94) (95) (96) (97) (98) (99) (100)	

Californium-252 Plasma Desorption Mass Spectrometer Data System

Background and Objectives: The Californium-252 time-of-flight (TOF) mass spectrometer employs nuclear fission fragments to ionize samples that frequently have proven intractable to other methods of analysis. In this instrument, fission fragments generated by the radioactive decay of a thin film of ²⁵²Cf impact on a thin layer of sample deposited on a conductive plastic film, producing a localized plasma. The sample molecules produced within this plasma are extracted by an electric field and briefly accelerated down an evacuated tube toward a microchannel plate ion detector. The elapsed times between the ionization event and the arrival of the ions produced are measured with an ultraprecise clock capable of measuring time intervals of hundreds of milliseconds with a resolution of 800 picoseconds. The elapsed time measurements are then sent to a computer where they are sorted, tallied, converted to mass units, and displayed. The extended range of the timing clock coupled with the unique characteristics of the ionization process make this mass spectrometer ideally suited to the investigation of the high molecular weight compounds typical of biological materials. The TOF mass spectrometer, which is not commercially available, was developed at Texas A & M University by Dr. Ronald Macfarlane under a NHLBI contract. The data system was specified to be compatible with interface hardware and software available from Dr. Macfarlane. The need for realtime sorting of a large volume of input data puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Realtime performance and the ability to access very large data arrays in main memory are key considerations.

Progress in FY82: After delays necessitated by hardware design problems, software upgrades, and facilities renovations, both the spectrometer and a data system modeled after one in use at Texas A & M University have been installed in the laboratory of Dr. Henry Fales, LC, NHLBI, and will soon be functional. This instrument will provide NIH the capabilities of mass analysis for compounds that have proven difficult or impossible to analyze by other mass spectrometric means, also extending the range of mass analysis to compounds with molecular weights in excess of 5000.

Proposed Course: Expansion of the computer system to include a line printer and additional memory is currently planned. Modifications to the mass spectrometer are also in progress to enhance its safety and reliability. Plans are being developed to implement computer control of sample changing as well.

Distributed Laboratory Data Acquisition and Control System

An integrated laboratory data acquisition and processing system has been developed for LCP and LMB, NIADDK. The system is configured with satellites coupled through a local network to a host processor. At each satellite a dedicated microcomputer system performs data acquisition from and control over an instrument/experiment. Although acquired data files may be stored locally, they are normally transferred via the network to a host storage medium. The local network allows the host storage medium to appear as a 'virtual' storage device to the satellites.

Background and Objectives: A system of microcomputers capable of independently controlling and acquiring data from an instrument/experiment was proposed in December 1976 as the best system architecture of upgrading laboratory data processing. A prototype laboratory data acquisition and control system (LDACS) computer and essential elements of the communication system were developed.

Satellites perform the realtime data acquisition and instrument control functions. Their configuration includes a Digital Equipment Corporation (DEC) LSI-11 microcomputer, a 28K word memory, low density random access storage, graphics terminal, and all the necessary I/O hardware to interface the instrument/experiment. Software developed by CSL for each satellite, running under DEC's RT-11 operating system, provides the user with a 'turn-key' system. Presently, the system is configured with eight satellites, supporting eleven instruments, connected (via the communications computer) to a DEC PDP11/70 host processor. Instruments connected to the network include: spectrophotometer, CARY 14, CARY 118, CARY 219, two Perkin-Elmer 580B's, a microspectrophotometer (designed by NIADDK); spectropolarimeters, CARY 60, Jasco J500A; a Varian Electron spin resonance spectrometer; I. S. Co. Model 1440 liquid chromatograph; and a stimulus response retina experiment.

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use data since)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00058-03 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (10 characters or less) Californium-252 Plasma Desorption Mass Spectrometer Data System		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: R. L. Tate, Ph.D. Computer Specialist CSL, DORT		
OTHER: H. M. Fales, Ph.D. Chief LC, NHLRI		
COOPERATING UNITS (1 to 7) LC, NHLRI		
LAB/BRANCH Computer Systems Laboratory		
SECTION Processor Design Section		
INSTITUTE AND LOCATION DORT, NIH, Bethesda, MD 20205		
TOTAL MANHOURS 4	PROFESSIONAL 4	OTHER
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEUTRON		
<input type="checkbox"/> (d) WINDS <input type="checkbox"/> (e) INTERVIEW		
SUMMARY OF WORK (200 words or less - underline keywords) The Californium-252 plasma desorption mass spectrometer puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Realtime performance and the ability to access very large data arrays in main memory are key considerations. After delays necessitated by hardware design problems, software upgrades, and facilities renovations, both the spectrometer and a data system design modeled after one in use at Texas A & M University have been installed and are now functional. This instrument now provides NIH the capabilities of mass analysis for compounds that have proven difficult or impossible to analyze by other mass spectrometric means. It also extends the range of mass analysis to compounds with molecular weights in excess of 5000.		

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(Rev. 2-81)

The local network includes a software module, installed as a handler under the RT-11 operating system, at each satellite. Each satellite is connected via a hardwired serial link to a front end communications computer. The communications computer performs a file store and forward function. Received files are placed on a first-in-first-out queue. Files are transferred from the queue to the host via a parallel DMA link. The communications task running on the host maps the files to the appropriate directory area based on the identity of the satellite that originated the transfer and the extension of the file being transferred.

The host processor, a DEC PDP 11/70, is configured with: 640K words of memory, a high speed printer/plotter, an X-Y plotter, a 9-track magnetic tape drive, dual floppy disk drives, and two large capacity disk drives. DEC's multiuser, multitasking operating system, RSX-11M, is used to service the processing needs of the users. User access to the host is provided by hardwired links between terminals and host timesharing ports. Processing software provided at the host allows LDACS data files to be: added, subtracted, averaged, smoothed, baseline corrected, integrated, differentiated, multiplied by a constant, and added to a constant. The results may be displayed graphically on a Tektronix terminal, typed at a terminal, printed on the line printer, plotted on an X-Y plotter or transmitted to the DECsystem-10 for additional processing.

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use data since)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00058-03 CSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (10 characters or less) Distributed Laboratory Data Acquisition and Control System		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI: J. L. Powell Electronics Engineer CSL, DORT		
OTHERS: W. W. Jennings Physicist LCP, NIAIDK E. R. O'Bryan Electronics Engineer CSL, DORT A. R. Schultz, Jr. Chief, Processor Design Section CSL, DORT		
COOPERATING UNITS (1 to 7) LCP and LMR, NIAIDK		
LAB/BRANCH Computer Systems Laboratory		
SECTION Processor Design Section		
INSTITUTE AND LOCATION DORT, NIH, Bethesda, MD 20205		
TOTAL MANHOURS 3.0	PROFESSIONAL 3.0	OTHER
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEUTRON		
<input type="checkbox"/> (d) WINDS <input type="checkbox"/> (e) INTERVIEW		
SUMMARY OF WORK (200 words or less - underline keywords) An integrated laboratory data acquisition and processing system has been developed for LCP and LMR, NIAIDK. The system is configured with satellites coupled through a local network to a host processor. At each satellite a dedicated microcomputer system performs data acquisition from and control over an instrument/experiment. Although acquired data files may be stored locally, they are normally transferred via the network to a host storage medium. The local network allows the host storage medium to appear as a "virtual" storage device to the satellites.		

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Progress in FY82: One new satellite, supporting a second Perkin-Elmer 580B spectrophotometer, was added to the system in FY82. LDACS software supporting the acquisition of ESR data versus time, and software supporting acquisition of MSP data versus wavelength (wavelength controlled by the LDACS) was added this fiscal year.

General processing programs were developed and installed for the PDP-11/70 allowing manipulation of LDACS data files and printing/plotting of the results. Special purpose programs were provided for processing of spectrophotometer melting run data and processing of data files from an MSP experiment.

The last vestige of the 11-year-old centralized data acquisition and processing system, the Honeywell-516 computer, was removed from the configuration.

User's manuals for the CARY 219, PE 580B's, and the stimulus response retina experiment were written under contract.

Documentation of minor modifications and additions to the software libraries developed for LDACS were completed under contract. Retrofitting of LDACS units was initiated with programs utilizing the software libraries and incorporating (where required) the multipurpose counter/timer module, and the temperature control unit (both developed by CSL).

Proposed Course: Support for the system will continue. The retrofitting of LDACS units with up-to-date software will be completed. Documentation of the system will be given a high priority, with the objective of completing an *LDACS User's Guide* for each LDACS and completing all systems documentation.

The original scope of the project (upgrading the H-516 centralized system) is approaching completion. However, it is anticipated that some level of long-term support will continue. New satellites or instruments may be added to the system, and existing LDACS acquisition programs may be modified to enhance data acquisition or to incorporate new instrument/experiment setups. Occasionally, special-purpose programs are required to process a set of experimental data.

Publication:

Powell, J. I., Fico, R., Jennings, W. H., O'Bryan, E. R., Schultz, Jr., A. R.: A Local Network for Distributed Laboratory Microcomputers. *Tutorial-Microcomputer Network*, 1981, pp. 263-268.

Image Processing Facility

This project is intended to provide a utility to display and analyze digital images. The system will consist of a powerful 32-bit computer with a mixture of medium- and high-resolution displays. Also, the system will include a microdensitometer to allow precise digitization of x-rays, micrographs, and other images. The computer and peripherals have been purchased, and construction of the physical space to house the system is complete. Procurement of the first of the displays is underway, with delivery expected early in FY83.

Background and Objectives: This project arose in response to a critically overcrowded situation that exists on the present DCRT Evans and Sutherland Graphics computer. As image processing applications at NIH have increased, the limited resources of that graphics system have been saturated. During FY80, CSL, in collaboration with present and potential users designed a new general-purpose computer facility to aid the acquisition, display, and analysis of images such as electron

CHRISTOPHER SCIENCE INFORMATION (ECONOMIC PROJECT NUMBER) (DO NOT USE THIS SPACE)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC SERVICE OFFICE OF RESEARCH INTERNATIONAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00064-03 CSL	
PERIOD COVERED October 1, 1981 to September 30, 1982					
TITLE OF PROJECT (50 characters or less) Image Processing Facility					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI:		D. Syed		Chief, Systems Design Section CSL, DCRT	
OTHERS:		W. L. Rizzo A. J. Pashayan B. Trus		Electronics Engineer Computer Specialist Research Chemist CSL, DCRT CSL, DCRT CSL, DCRT	
COOPERATING UNITS (if any) None					
LAB/BRANCH Computer Systems Laboratory					
SECTION Systems Design Section					
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205					
TOTAL MANPOWER:		2		PROFESSIONAL: 2 OTHER: 0	
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN ISSUES <input type="checkbox"/> (c) NEITHER					
<input checked="" type="checkbox"/> (a) WINDS <input type="checkbox"/> (a2) INTERVIEW					
SUMMARY OF WORK (200 words or less - underline key words) This project is intended to provide a utility to display and analyze digital images. The system will consist of a powerful 32-bit computer with a mixture of medium and high resolution displays. Also, the system will include a microdensitometer to allow precise digitization of x-rays, micrographs and other images. The computer and peripherals have been purchased, and construction of the physical space to house the system is complete. Procurement of the first of the displays is underway, with delivery expected early in FY83.					

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(Rev. 2-81)

CHRISTOPHER SCIENCE INFORMATION (ECONOMIC PROJECT NUMBER) (DO NOT USE THIS SPACE)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC SERVICE OFFICE OF RESEARCH INTERNATIONAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00097-01 CSL	
PERIOD COVERED October 1, 1981 to September 30, 1982					
TITLE OF PROJECT (50 characters or less) Analytic Models of Computer System Performance					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI:		R. L. Martino		Electronics Engineer CSL, DCRT	
OTHER:		R. W. Newcomb		Professor, Electrical Engineering Department Univ. of MD	
COOPERATING UNITS (if any) University of Maryland					
LAB/BRANCH Computer Systems Laboratory					
SECTION Systems Design Section					
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205					
TOTAL MANPOWER:		0, 2		PROFESSIONAL: 0, 2 OTHER: 0	
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN ISSUES <input type="checkbox"/> (c) NEITHER					
<input checked="" type="checkbox"/> (a) WINDS <input type="checkbox"/> (a2) INTERVIEW					
SUMMARY OF WORK (200 words or less - underline key words) This project involves the development of analytic models that can be used to evaluate the performance of computer systems. During the past year, tools for modeling and analyzing computer systems using the graph theoretic model called Timed Place-Transition (P-T) nets were developed. This included the introduction of four special nodes, the determination of new methods for finding net invariants, and the derivation of new relationships among net variables from net structure. Using these results, a method was developed for evaluating computer system performance with Timed P-T Net models. This method was used to model and analyze the bus arbitration techniques that occur in digital systems. In addition, a state variable P-T Net model of the interconnection of two or more microprocessors was developed. This model provides a framework for determining the avoidance of deadlock and the maintenance of throughput in multiple microprocessor systems. In FY83, this work with Timed P-T Nets will be continued.					

PH-6540
(Rev. 2-81)

micrographs, CAT scans, and radiographs. This facility will be available for use by the NIH community.

Progress in FY82: The system will be based on a 32-bit, one megabyte computer, with a smaller 16-bit processor to handle image acquisition. A multidisplay raster scan frame buffer will provide several users concurrent access to the central processor. Images will be digitized when necessary through a microdensitometer or a vidicon camera. Hard copy will be provided by a camera system.

All currently budgeted equipment and software have been ordered; some already has been received and the rest is scheduled for delivery in the next few months. The physical space has been completed with all power and cooling.

Significance to Biomedical Research: Study of images obtained in the biomedical laboratory is able to supply the proper tools at a reasonable cost. Biomedical scientists are employing image analysis for a wide variety of research goals, and the use of such techniques is expected to grow very rapidly in the near future.

Proposed Course: As the equipment is delivered, it will be integrated into a system. The development of systems and applications software, as well as the transfer of existing image packages from the Evans and Sutherland system, will proceed.

Analytic Models of Computer System Performance

This project involves the development of analytic models that can be used to evaluate the performance of computer systems. During the past year, tools for modeling and analyzing computer systems using the graph theoretic model called Timed Place-Transition (P-T) Nets were developed. This included the introduction of four special nodes, the determination of new methods for finding net invariants, and the derivation of new relationships among net variables from net structure. Using these results, a method was developed for evaluating computer system performance with Timed P-T Net models. This method was used to model and analyze the bus arbitration techniques that occur in digital systems. In addition, a state variable P-T Net model of the interconnection of two or more microprocessors was developed. This model provides a framework for determining the avoidance of deadlock and the maintenance of throughput in multiple microprocessor systems. In FY83, this work with Timed P-T Nets will be continued.

Background and Objectives: There are two major approaches to evaluating the performance of a computer system: simulation and analytic modeling. Simulation models have been a popular form of modeling for years but can be difficult and costly to construct, validate, and run. Recent advances in analytic modeling techniques, which can be used to model many aspects of a computer system, have provided new tools for evaluating computer system performance.

There are two major types of analytic modeling techniques: graph theoretic and queueing theory models. A number of graph theoretic models have been found to be useful for the analytic modeling of computer systems. These include such graph models as Place-Transition (Petri) Nets, Parallel Program Schemata, Computation Graphs, and Marked Graphs. Queueing theory models have also been found to be useful for the modeling of computer systems because they can capture important features of actual systems, and algorithms that solve the equations of these models are available as queueing network evaluation packages.

These analytic models provide useful tools when designing computer systems and deciding among alternative hardware or software configurations. In particular, with the integrated circuits that are currently available, it is technically and economically feasible to build systems consisting of many central processing units. Many processor and memory configurations also are possible now that memories can be placed in close proximity to the processors. Methods are needed for designing systems now possible with this new technology. Various structures must be considered and analytic methods for evaluating alternatives must be developed.

Methods Employed: Timed Place-Transition (P-T) Nets are the modeling technique used to develop tools for evaluating computer system performance. The advantages of modeling with these nets are that: large and complex systems can be represented in a manner that is easy to understand due to the graphical and precise nature of these nets; the behavior of the modeled system can be analyzed using developed results of the P-T Net theory; and a system can be synthesized hierarchically with the ability to use different levels of abstraction and refinement. In addition, the usefulness of P-T Nets as models results from their ability to represent both concurrency and conflict in a system. Concurrency occurs when more than one event is taking place in a system at one time and conflict occurs when a decision must be made among alternatives. In order to evaluate the performance of computer systems

including such things as waiting times and throughputs, the time parameter is added to the P-T Net model.

Progress in FY82: During the past year, tools for modeling and analyzing computer systems using Timed P-T Nets were developed. This included the introduction of four special nodes, the determination of new methods for finding net invariants, and the derivation of new relationships among net variables from net structure. Using these results, a method was developed for evaluating computer system performance with Timed P-T Net Models. This method was used to model and analyze the bus arbitration techniques that occur in digital systems. From these models, important upper bounds on the average time a device waits for the bus and the average time the shared bus is not used were derived. This work demonstrates that the results that can be obtained concerning the performance of a computer system using Timed P-T Net models is

dependent on the structure of the net that accurately portrays the system.

A state variable P-T Net model of the interconnection of two or more microprocessors with input and output devices was developed. This model provides a useful framework for modeling and analyzing multiple microprocessor systems. For example, it can be used to determine the avoidance of deadlock and the maintenance of throughput in such systems.

Proposed Course: The work on using Timed P-T Net models for evaluating computer system performance will be continued, including the derivation of more relationships among net variables based on the structure of these nets and the development of a Timed P-T Net model where time is associated with both the places and transitions of the net. Also, this graph theoretic model will be compared with queueing theory models of computer system performance.



Laboratory of Applied Studies

Eugene K. Harris, Chief

Clinical Research and Patient Care

Computer-aided analysis of electrocardiograms.

J. Bailey, M. Horton (LAS); cardiologists and biomedical engineers in the U.S.A. and abroad. The purpose of this project is to evaluate the utility of leading computer programs for ECG interpretation, and to search for optimal computer-based methods of extracting medically significant ECG patterns. A study of the components of variance in ECG parameters has been completed, using data from the Framingham Heart Project; a manuscript is being prepared.

Computer systems for nuclear medicine. J. Bailey, M. Douglas, R. Burgess (LAS); H. Ostrow (CSL); M. Green, et al. (CC, Nuclear Medicine). This project involves development and application of computer systems to such diagnostic imaging activities as ECG-gated radionuclide ventriculography and dynamic scintigraphic studies of other organs (e.g., kidneys, lungs). A study of 79 radionuclide ventriculograms has revealed average signal-to-noise characteristics, optimum filtering, and optimum segmentation for detection of regional abnormalities; a series of manuscripts is being prepared. A study of segmental artery stenosis in canines using functional maps of renal scintigraphic data has been published.

Computer-based studies of pulmonary pathophysiology and respiratory disease. J. Bailey, R. Burgess, M. Horton, E. Pottala (LAS); R. Crystal, A. Nienhuis (NHLBI); A. Jones (CC, Nuclear Medicine). These studies attempt to achieve better understanding of pulmonary pathophysiology through use of computer-based models of pulmonary gas exchange and respiratory mechanics, comparing predicted values with real patient data. A minicomputer-based system for analyzing gas exchange during exercise was purchased and installed. Development of programs to analyze mass spectrometer and flowmeter data and to control the treadmill and bicycle is nearly complete.

Statistical research in clinical pathology. E. Harris, M. Horton, A. Albert (LAS); G. Shakarji, F. VanSant (DMB); clinical chemists and others in the U.S.A., Europe, and Japan. This research involves application of statistical theory to clinical laboratory tests, including serial studies of blood chemistries in health and disease. Multivariate subject-specific reference regions were shown by computer simulation studies and applications to real data to be substantially more specific against false positive results than corresponding univariate reference ranges. A collaborative study to explore relative sensitivities in various diseases has begun. A statistical method for deriving reference differences as criteria for evaluating the significance of observed changes has been extended and applied to a comprehensive data base of serial data from healthy subjects. A method for sequential assessment of risk in acute disease has been developed by combining discriminant function with analysis of response curves. The method has tested successfully in application to patients under intensive care following myocardial infarction.

Computer-based studies in ultrasonography. M. Douglas, J. Bailey, E. Pottala (LAS); B. Maron (NHLBI). Ultrasonography allows noninvasive visualization of many organs without the hazard of ionizing radiation. This project involves development of minicomputer systems for image enhancement, pattern recognition, and three-dimensional reconstruction from ultrasound data sources, principally wide-angle phased array echocardiography. A principal difficulty in echocardiogram studies is separating gross cardiac motion from regional wall movement in a quantitative way. To resolve this problem, we have begun to study the use of reliable fiducial points, such as the papillary muscles or the intersection of mitral cusps. Further progress in this project awaits upgrading of the DeAnza system by the vendor.

Laboratory Investigation

Mathematical modeling of biological processes.

J. Fletcher (LAS); R. Schubert (Louisiana Tech. University). Scientists are developing and applying mathematical models in studies of substrate transport in the microcirculation, in diffusion processes in physiology, and in macromolecule-ligand binding equilibria. A new unified model has been developed for the microcirculation during a perfused organ experiment. Parametric studies of this model's properties are underway. A final summary report on mathematical models for equilibrium binding experiments was published and distributed. A new investigation of capillary hematocrit and oxyhemoglobin unloading effects in capillaries was begun.

Mechanisms of active transport/biochemical kinetics.

B. Bunow (LAS); A. Kaplan (NCI); D. Mikulecky (Medical College of Virginia); J. Kernevez (University of Tech., Compiègne, France). Experimental and mathematical studies of the energy mechanisms for active transport and of multistate biochemical kinetics in cells and membranes continue. Network modeling methods were applied through collaboration with NIH scientists to problems including cellular metabolism, neural networks, nerve conduction, and tissue oxygenation. A realistic mathematical model for isoelectric focusing has been derived and programmed for computer solution.

Hybrid computing to analyze physiologic signals and construct simulation models.

E. Pottala, B. Bunow (LAS); T. Colburn (NIMH); various NIH and FDA scientists. This project uses the LAS minicomputer system (MAC-16) for hardware simulation of physiologic functions and for analysis of analog signals (myogram, EEG, etc.). Two network simulation languages were implemented on the IBM System 370 and the VAX system (NIMH). This will facilitate model building and make simulation models more accessible for investigators on campus.

Image processing in electron-loss spectroscopy.

M. Douglas, (LAS); J. Costa (NIMH). This project involves the development and implementation of mathematical models and image enhancement techniques to analyze computer-acquired information from electron-loss and x-ray spectra indicating the location of extremely small quantities of important chemical elements and active protein molecules within cells. Activities in this area have been delayed while the vendor completes upgrading of the DeAnza system as originally planned.

Computer Research and Development

Mathematical and computational methods for nonlinear equations.

R. Shrager, R. Hendler (NHLBI); A. Schechter (NIADDK). Work continues in the study of methods of fitting nonlinear models and mathematical methods of spectral analysis. An algorithm was developed for rapid solution of one nonlinear equation in one unknown. The method does not require derivatives and guarantees the answer to full machine precision. The algorithm has been installed in MLAB. A program to simulate the oxygen saturation of hemoglobin from the primary regulators pH, PCO₂, and 2,3-DPG is now under development. Also under development is a program to optimize the wavelength selection in the design of hemoglobin saturation analyzers.

Numerical methods for the solution of mathematical models describing reaction-diffusion and other processes in biological systems.

M. Bieterman, J. Fletcher, B. Bunow (LAS); I. Babuska (University of Maryland). Ongoing study, development, and implementation of efficient, flexible numerical methods for the solution of nonlinear ordinary and partial differential equations is involved in modeling dynamic physiological processes. Theoretical work was completed on the adaptive finite element method for solving systems of reaction diffusion equations. Program packages have been implemented on the IBM System 370 and are currently undergoing testing. Preliminary applications have been made to problems in nerve conduction, facilitated diffusion in tissues, developmental biology, and ecosystems.

Research Projects

Statistical Research in Clinical Pathology

Univariate and multivariate time series models and discriminant techniques are being applied to various data bases consisting of short series of measurements of serum biochemistries in healthy subjects and patients with myocardial infarction. The purpose is to gain practical experience in the use of these statistical predictive techniques to detect changes and trends within individuals, taking into account biological variation and measurement error. The time scale of these series varies from daily to weekly, 6-month, and 12-month intervals between observations. Parallel computer-based simulation studies are also underway, particularly to estimate the relative sensitivities and specificities of multivariate and univariate forecasting methods. Mathematical investigations into the properties of a new stochastic model of linear change are continuing.

INTERNATIONAL SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (FOR USE BY THIS CENTER)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE OFFICE OF INTERNATIONAL RESEARCH PROJECT	PROJECT NUMBER
		DOT 070000/7-14 LAD
PERIOD COVERED	October 1, 1981 to September 30, 1982	
TITLE OF PROJECT (40 characters or less)	Statistical Research in Clinical Pathology	
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI:	K.K. Harris	Chief, Lab. of Applied Studies LAD, DORT
OTHERS:	A. Albert	Fogarty International Research Fellow (Belgium) LAD, DORT
	J. Smarzynski	Supr. Systems Analyst JMS, DORT
	A.B. Norton	Computer Systems Analyst LAD, DORT
	E. Ziss	Clinical Pathology TC
	G.Z. Williams	Institute for Health Sci. Francisco, CA
	T. Yasaka	PL Medical Service Dept. Osaka, Japan
COOPERATING UNIT: (if any)		
None		
LAB/SEARCH Laboratory of Applied Studies		
SECTION		
INSTITUTE AND LOCATION (CITY, STATE, ZIP CODE)		
DORT, W.L., Bethesda, MD 20205		
TOTAL MANPOWER		
PROFESSIONAL		
OTHER		
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN ISSUES <input type="checkbox"/> (c) NEITHER		
<input checked="" type="checkbox"/> (d) WINDS: (a) INTERVIEW:		
SUMMARY OF WORK (200 words or less - underline keywords): Univariate and multivariate time series models and discriminant techniques are being applied to various data bases consisting of short series of measurements of serum biochemistries in healthy subjects and patients with myocardial infarction. The purpose is to gain practical experience in the use of these statistical predictive techniques to detect changes and trends within individuals, taking into account biological variation and measurement error. The time scale of these series varies from daily to weekly, 6-month, and 12-month intervals between observations. Parallel computer-based simulation studies are also underway, particularly to estimate the relative sensitivities and specificities of multivariate and univariate forecasting methods. Mathematical investigations into the properties of a new stochastic model of linear change are continuing.		

PROJECT: (New, Exis)

Objectives: To investigate applications of statistical theory, particularly the use of variance components, discriminant analysis, and the theory of discrete and continuous time series, to the interpretation of serial clinical laboratory measurements in healthy subjects and patients with acute and chronic disease.

Progress during FY82: The study of the relative specificities of univariate and multivariate reference regions, applied to subject-specific serial observations, has been completed and published. Results from computer simulations were confirmed by analysis of semiannual series of clinical chemistry measurements in 700 longterm participants in health maintenance programs in Tokyo and Osaka, Japan. Multivariate reference regions were shown to be much more specific than corresponding univariate regions, thus capable of avoiding many false alarms. A statistical comparison of regional data bases of clinical chemistries in healthy individuals has begun. This work is part of a general investigation into the transferability of clinical data among population groups and geographic areas.

New research was undertaken on the development and application of a statistical method for estimating 'reference changes,' that is, critical differences between successive measurements of a biochemical constituent in an individual. At the present time, such criteria are left to the judgement of the individual physician and are known to vary widely even among residents in the same hospital. The proposed method, allowing for serial correlation, has been tested on serial observations of calcium and alkaline phosphatase in healthy subjects. A paper describing the method and its uses is in preparation.

The main research project under A. Albert's Fogarty International Research fellowship has been concerned with the development and testing of models to assess changing risk probabilities in patients with acute diseases. Several methods have been proposed and successfully applied to existing data bases of patients with acute myocardial infarction, and children treated in intensive care units. Besides this project, Dr. Albert has also undertaken studies on ways to improve laboratory data interpretation and made available to the NIH research community a program for multiple group logistic discrimination.

Proposed Course: A study of the relative sensitivity of multivariate reference regions will be initiated in collaboration with Dr. Yasaka. This will entail incorporating into the data bank followup information on the clinical status of individuals examined.

Further development and application of the statistical methodology proposed for calculation of reference changes will be undertaken for selected patient groups in collaboration with members of the Clinical Pathology Department at the University of Virginia Medical School. Continued joint efforts in this area and in the general application of stochastic time series to patient data will be initiated with Dr. Albert, Fogarty Research Fellow in this Laboratory, upon his return in 1982 to the University of Liege.

The statistical comparison of regional data bases in Japan will continue.

Publications:

- Albert, A.: Atypicality indices as reference values for laboratory data. *Amer. J. Clin. Pathol.* 76: 421-425, 1981.
- Albert, A.: Discriminant analysis based on multivariate response curves: an approach to dynamic prognosis. *Statistics in Medicine* (in press).
- Albert, A.: On the use and computation of likelihood ratios in Clinical Chemistry. *Clin. Chem.* 5: 1113-1119, 1982.
- Albert, A., Chapelle, J.P., Heusghem, C., Kulbertus, H.E., and Harris, E.K.: Evaluation of risk using serial laboratory data in acute myocardial infarction. In Heusghem, C., Albert, A., and Benson, E.S. (Eds.): *Advanced Interpolation of Clinical Laboratory Data*. New York, Marcel Dekker (in press).
- Harris, E.K.: Further applications of time series analysis to short series of biochemical measurements. In Grasbeck, R., and Alstrom, T. (Eds.): *Reference Values in Laboratory Medicine*. Chichester, U.K., John Wiley & Sons, 1981, pp. 167-176.
- Harris, E.K.: Regression, least squares, and correlation. In Seligson, D., M.D. (Ed.): *Handbook of Clinical Chemistry*. CRC Press (in press).
- Harris, E.K.: Use of statistical models to detect subject specific changes. In Yasaka, T. (Ed.): *Proceedings of the International Conference on Automated Multiphasic Health Testing & Services*. Amsterdam, Excerpta Medica, 1981, pp. 35-44.
- Harris, E.K., Yasaka, T., Horton, M.R., and Shakarji, G.: Comparing Multivariate and Univariate subject-specific reference regions for blood constituents in healthy persons. *Clinical Chemistry*, 28: 422-426, 1982.

Mathematical Models of Binding Equilibria

The objective of this project is the study of mathematical models of ligand-receptor or ligand-macromolecule binding studies at equilibrium. The models are examined for mathematical as well as for conceptual validity and are studied to determine their suitability for fitting to experimentally obtained laboratory data. The appropriateness of various model fitting criteria are studied and general guidelines and computational algorithms are designed for computer-aided interactive model fitting.

Progress in FY82: Numerous requests for copies of exportable computer algorithms were honored and a number of B/I/D consultations were provided. A summary report including collected results from fifteen years of research in this area was completed. It is now available for general distribution to the biomedical community.

Proposed Course: Applications of existing and new methodology to data analysis will continue to be made as they are requested by collaborating laboratories. Computer programs, reprints, and reports continue to be provided to requesting consultees. Analytical development of new models and continued research in fitting methodology in this area will emphasize validation of experimental techniques, multi-receptor models, and conformational changes in macromolecules due to binding of ions.

Publications and Abstracts:

- Fletcher, J. E.: *The Analysis of Equilibrium Binding Data by the Fitting of Models*. July 1982.

Mathematical Modeling of Substrate Transport in Physiological Environments

Mathematical models of microcirculatory structure and function are developed from conceptual models into systems of coupled ordinary and/or partial differential equations. Methods of solution of these nonclassical formulations are developed and tested and satisfactory cost effective methods are used to explore the properties of these models. The results are interpreted in terms of microcirculatory physiology and are published in the scientific literature.

INTECHNOLOGY DESIGN INFORMATION LEADSHIPS PROJECT NUMBER (Do not use this space)	N.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL CENTER FOR HUMAN RESEARCH PROJECT	PROJECT NUMBER 201 C720005-12 LAG
PERIOD COVERED October 1, 1981 to September 30, 1982 TITLE OF PROJECT (40 characters or less) Mathematical Models of Binding Equilibria		
NAME, LABORATORY AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT PI: J.E. Fletcher Chief, Applied Mathematics Section LAG DCMT UTMERS: R. Shragser Mathematician, AMC LAG DCMT P. Abraham Visiting Scientist (C.W. University) NC1 J. Dunn Physical Chemist Laboratory of Carcinogenesis NC1		
COOPERATING UNIT: (a + b) NONE		
LAB/BRANCH Laboratory of Applied Studies SECTION Applied Mathematics Section INSTITUTION AND LOCATION DCMT, NIH, Bethesda, MD 20205 FUND. MONITORING U-5 PROFESSIONAL OTHER CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NUTRITION <input type="checkbox"/> (d) DRUGS <input type="checkbox"/> (e) INTERVIEW SUMMARY OF WORK (200 words or less - underline keywords) The objective of this project is the study of mathematical models of ligand-receptor or ligand-macromolecule binding studies at equilibrium. The models are examined for mathematical as well as for conceptual validity and are studied to determine their suitability for fitting to experimentally obtained laboratory data. The appropriateness of various model fitting criteria are studied and general guidelines and computational algorithms are designed for computer-aided interactive model fitting.		

PG-6402
(Rev. 2-78)

INTECHNOLOGY DESIGN INFORMATION LEADSHIPS PROJECT NUMBER (Do not use this space)	N.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL CENTER FOR HUMAN RESEARCH PROJECT	PROJECT NUMBER 201 C720005-14 LAG
PERIOD COVERED October 1, 1981 to September 30, 1982 TITLE OF PROJECT (40 characters or less) Mathematical Modeling of Substrate Transport in Physiological Environments		
NAME, LABORATORY AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT PI: J.E. Fletcher Chief, Applied Mathematics Section LAG DCMT UTMERS: R.W. Schubert Assoc. Prof. Louisiana Tech Univ. Dept. of Biomedical Engineering N. Rafterman Mathematician, AMC LAG DCMT S. Duling Professor of Physiology Charlottesville, VA Medical School		
COOPERATING UNIT: (a + b) NONE		
LAB/BRANCH Laboratory of Applied Studies SECTION Applied Mathematics Section INSTITUTION AND LOCATION DCMT, NIH, Bethesda, MD 20205 FUND. MONITORING U-5 PROFESSIONAL OTHER CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NUTRITION <input type="checkbox"/> (d) DRUGS <input type="checkbox"/> (e) INTERVIEW SUMMARY OF WORK (200 words or less - underline keywords) Mathematical models of microcirculatory structure and function are developed from conceptual models into systems of coupled ordinary and/or partial differential equations. Methods of solution of these non-linear formulations are developed and tested and satisfactory cost effective methods are used to explore the properties of these models. The results are interpreted in terms of microcirculatory physiology and are published in the scientific literature. One objective of this project is to study whole organ and organ tissue level phenomena by means of mathematical models in an effort to determine relationships between variables that govern the organ response to physiologic challenges.		

PG-6402
(Rev. 2-78)

One objective of this project is to study whole organ and organ tissue level phenomena by means of mathematical models in an effort to determine relationships between variables that govern the organ response to physiologic challenges.

Progress in FY82: The details of a new, intricate, mathematically correct, solution to the generalized Krogh cylinder model were completed. A second effort was begun to investigate the kinetics of red cell and free hemoglobin offloading during capillary transit. This work is still in the exploratory stages. A manuscript describing the first effort has been accepted for publication. Two preliminary reports on the findings from these studies were presented at international meetings.

It is anticipated that the research course of this project will have the following stages.

1. Reexamine the Krogh cylinder models in the literature and their adequacy for the representation of perfused organ microcirculation.
2. Develop exact mathematical solutions for extended Krogh models that exhibit tissue axial diffusion and capillary axial diffusion for the steady state constant metabolic rate experiments with perfused organs.
3. Develop or modify numerical algorithms that will compute substrate levels for nonconstant metabolic rates and other nonlinear effects.
4. Develop algorithms for the direct comparison of distributed substrate level computations with experimentally obtained microelectrode measurements.
5. Identify those critical ranges of parameters that control organ response to physiologic challenge.

Publications and Abstracts:

Fletcher, J.E.: Diffusional Transport Coupling in an Ideal Capillary Tissue Structure. SIAM 30th Anniversary Meeting, Stanford University, 1982.
 Fletcher, J.E., and Schubert, R.W.: On the Computation of Substrate Levels in Perfused Tissues. *Mathematical Biosciences* (in press).
 Fletcher, J.E., and Schubert, R.W.: The Theoretical Prediction of Substrate Levels and Their Histograms in Cell Free Perfused Tissues. *Proceedings of the International Meeting of the OTT Society*, Detroit, Michigan, August 1981, Plenum Press (in press).
 Schubert, R.W., Fletcher, J.E., and Rneau, D.D.: A Simplified Model for Predicting Myocardial PO₂ Histograms. The First Southern Biomedical Engineering Conference, LSU Medical Center, Shreveport, LA, 1982.

Analysis of Coupled Transport and Biochemical Kinetics

This project investigates six fundamental problems in biology: (1) the role of dynamic patterns in embryology and evolution, (2) the kinetics of enzymes located in cell membranes, (3) the kinetics of enzymes derived from malignant and normal cells in culture, (4) mathematical modeling of isoelectric focusing studies, (5) thermodynamics of bioenergetic mechanisms in mitochondria, and (6) development of a new paradigm for biological modeling based upon topological representation and use of network modeling languages. Simulation on digital computers, particularly with network modeling languages, numerical solution of differential equations, and nonlinear regression analysis are the main tools in these investigations. While these problems are diverse in their biological background, they all share in a common basis of mathematical and physical content through the role played by conservation laws and the mathematical methods involved in their resolution.

- **Dynamic Patterns**

Progress in FY82: This project is now essentially complete. Two manuscripts are still in press.

- **The Kinetics of Enzymes in Membranes**

Background and Objectives: Studies of the mechanism of membrane transport and energy transduction by membranes are generally less conclusive than studies of the mechanisms of enzymes in solution. This uncertainty arises because it is difficult both to manipulate the environment of the interior of a biological membrane and to measure responses there. The objective of this project is to determine the extent to which the actual organization of membrane-associated processes can be correctly inferred from the application of models to the kinds of experimental measurements currently made.

Significance for Biomedical Research: Studies of membrane-associated enzymes, such as those of mitochondria, for example, are made by measuring external concentration changes, from which one attempts to infer biochemical organization. This process is quite unreliable, as witnessed by the continuing controversy over the biochemical organization of bioenergetics. By our work, we wish to demonstrate that this unreliability is intrinsic, that it results from the nature of the methods used to study such systems, and that it is not to be remedied by performing yet another experiment of the kinds currently popular, no matter how ingenious.

Progress in FY82: An experimental system involving an enzyme immobilized in a polymer film had been previously prepared and studied. A manuscript describing the behavior of this system has been completed and will soon be submitted. This project is now complete.

- **Kinetics of Lactate Dehydrogenase (LDH) from Normal and Malignant Hepatocytes**

Progress in FY82: The major collaborator in this project has been inactive this year because of complications associated with a move to a new laboratory in Frederick.

Future Course: During FY83 the computer system will be installed in the new lab. Hopefully the experimental program can be reactivated.

- **Mathematical Modeling of Isoelectric Focusing**

Background and Objectives: Isoelectric focusing is a very widely employed experimental tool in biochemistry. Its purpose is to separate and identify the protein components of mixtures, e.g., the extracted contents of cells and tissues. Despite the effectiveness of currently used procedures, the application of isoelectric focusing proceeds on an ad hoc basis, and it is quite likely that these current procedures are less than optimal. The goal of this research is to place isoelectric focusing on a firm footing of physical chemistry through the derivation and solution of predictive equations to describe the process and its dependence upon experimentally controllable parameters.

Significance to Biomedical Research: Separation of proteins has an important role in the preparation of biologicals such as enzymes and vaccines for medical research and treatment. Improvement in the techniques of separation will lead to reduced expense for production of these materials and increased supplies and variety. Identification of proteins plays an essential role in diagnostic clinical chemistry as well as basic biological research. Improvement in identification procedures by reducing the sample size or time to resolution will permit more extensive studies on precisely defined preparations.

Progress in FY82: The physical-chemical principles involved in isoelectric focusing have now been identified. The mathematical equations turn out to be highly coupled, nonlinear partial differential equations

with very unusual boundary conditions. A FORTRAN program providing for numerical solution of these equations has been developed but not completely debugged. Unfortunately, the computer time to run this program was too great to permit its completion with the scheduling algorithm in place on the DCRT computer during FY82.

Future Course: The scheduling algorithm on the DCRT computer has been modified to permit efficient running of the FORTRAN program. The program will be completed to the point of verification of its functional correctness. Run time for production using the program will still be too excessive to permit extensive studies. A Cray-1 computer in France is to be used for preliminary production runs.

- **Thermodynamics of Bioenergetic Systems**
Background and Objectives: The mechanism by which the generally reduced components of nutrients are oxidized in mitochondria is still quite obscure, although most of the components of this pathway have been identified. The membrane association of the components of the pathway makes it difficult to proceed in the usual biochemical manner of molecular dissection and reconstitution. Most experimental studies are made on systems that are quite structurally complex. Nevertheless, interest focuses on the usual biochemical question: What is the sequence of molecular forms involved in the bioenergetic pathway? The role of ubiquinone in this pathway is the particular object of our interest in this project.

Significance to Biomedical Research: An understanding of the mechanism of the central energy-yielding process of living organisms is clearly essential. Thermodynamic analysis has shown that the accepted explanation for oxidant-induced reduction of cytochrome b in the presence of antimycin cannot be correct. Thermodynamic analysis combined with new experimental techniques developed by one collaborator (R. Hendler), and analyzed with methods developed by another collaborator (R. Shrager), promises to provide a basis for a correct explanation of this phenomenon.

Progress in FY82: During this year, the problem was identified, and the thermodynamic inconsistency of the current models for oxidant-induced reduction of cytochrome b was demonstrated. This work has been presented in seminar form, and a manuscript is in preparation.

Future Course: During FY83, we will attempt to provide an explanation that is consistent with thermodynamics, and to design and perform experiments to test its correctness. These experiments will be based on the recently

demonstrated ability to characterize small spectral shifts in cytochromes undergoing conformational change.

- **Network Modeling in Biology**

Background and Objectives: Mathematical modeling in biology is especially difficult because of the need to be familiar with both the biological basis of problems and the mathematical tools required for their solution. Network modeling, supplemented with effective modeling languages, largely obviates the need for extensive mathematical sophistication, and makes the process of modeling accessible to biologists lacking such skills. Topological modeling is particularly appropriate to biological problems because the objects of study generally satisfy conservation laws. In biological systems, the processes of flow, accumulation, and transformation are fundamental; these are likewise the basic operations in network modeling.

Significance for Biomedical Research: The choice of a model for a biological process strongly conditions the design of experiments to confirm and extend it. By making the analysis of models sufficiently simple, we intend to permit an investigator the freedom to consider many models. From comparisons among the models using simulation, it should be possible to develop incisive experiments that permit scientifically valid, rather than arbitrary, selection among the models. The network languages nicely complement the MLAB system in permitting users to model phenomena that are too complex to be conveniently described in MLAB.

Progress in FY82: Demonstration studies on network modeling have been conducted in several areas: (1) oxygen distribution and uptake in capillary beds, (2) nerve impulse transmission in an axon model, (3) electrical excitation of synaptic membranes, (4) electrotonic excitation of dendritic trees, and (5) metabolic networks in brain tumors. These studies have shown that functional and correct models can be constructed quickly and easily. By using available network modeling languages, the process of model building is focused on structures readily understood by biological investigators, rather than on verification of mathematical aspects. Several of these studies will prove to be directly useful in subsequent biological investigations. The network language, SPICE2, has been installed on a dedicated minicomputer in NINCDS. A course in SPICE2 programming for neurophysiologists was delivered to representatives from several labs in this institute. Network models are now being regularly employed in their research. The demonstration studies described above will be described in manuscripts in

preparation, and the monograph on topological modeling is well underway.

Future Course: During FY83, collaboration with groups using network modeling will continue. The DCRT course in network modeling will be repeated. The monograph should be completed this year. A major deficiency of available network languages is in the area of data fitting. A major effort will be made to facilitate the interconversion of models expressed in network terms into forms compatible with languages such as MLAB on which data fitting is convenient. DELIGHT, an extension of SPICE with facilities for optimization, device libraries, and more effective graphics, has been ordered and will be installed in FY83.

Publications:

Bunow, B.: All things flow and change--some thoughts on the role of reaction and transport in biology. *J. Wash. Acad. Sci.* (in press).
 Bunow, B.: Turing and the physico-chemical basis of biological patterns. In Prewitt, J. (Ed.): *IEEE Turing Memorial*. 1982 (in in press).
 Bunow, B., and Mikulecky, D.C.: On the feasibility of using flux measurements to distinguish among active transport models. *Polish Winter School of Membrane Transport*, (in press).
 Bunow, B., and Mikulecky, D.C.: Where does metabolic energy couple into the active transport process? *J. Theor. Biol.* (in press).

Nonlinear Equations

Methods are developed for solving nonlinear equations frequently encountered at NIH, usually in the context of constrained nonlinear least squares or in the solution to nonlinear differential equations. Related problems, such as asymptotic error analysis, and the efficient treatment of sparse systems, are also considered.

Progress in FY82:

• MLAB Projects

Gary Knott (DCRT). The root-finder has been refined so that it performs more efficiently than the best previously published methods. A paper has been submitted to *Mathematics of Computation* describing the procedure and the test results. A separate integration routine, independent of the differential equation solver, has been installed, so that integral expressions may now appear in differential equations. Some problems with the curve-fitter, reported by MLAB users, have been traced to poor scaling of the problem (e.g., unfortunate combinations of large and small effects of changing this or that parameter). A rescaling procedure is being designed to overcome the difficulty.

• Equilibrium Studies of Magnesium Phosphate Lev Jacobson (DCRT). Improved range of experimental data has enabled us to produce a simple yet adequate model of Mg-H-HP04 binding with reliable equilibrium constants. A manuscript detailing this work has been submitted for publication. Our contribution described how to propose alternate physical models, express them in reliably computable form, and suggest experiments for model validation.

• Hemoglobin Projects

Robert Berger (NHLBI); Robert Winslow (CDC Atlanta); Luige Rossi-Bernardi, Giulio Dossi, Michele Samaja, and Massimo Luzzana (Ospedale San Raffaele, Milan, Italy).

1. Two possibly conflicting criteria govern the design of a hemoglobin analyzer (design being the selection of wavelengths of light to best detect various binding states of Hb). The first, the product of variances of estimated fractions of the various states, is designed to reduce variance from random errors in the data. The second criterion, norm of the sensitivity matrix, is designed to minimize the effect of instrumental drift (aging, misalignment, etc.), which is very important because it cannot be 'averaged out' by repeated measurements. Procedures are now being tested that minimize either criterion or a weighted sum of both.

INFORMATION SOURCE INFORMATION EXCHANGE PROJECT NUMBER (10 AND 100 series) 100-000000-00 LAS		ALL DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF SERVICE INFORMATION RESEARCH PROJECT	PROJECT NUMBER 201 0700055-06 LAS
PERIOD COVERED October 1, 1981 to September 30, 1982			
TITLE OF PROJECT (40 characters or less) Analysis of Coupled Transport and Biochemical Kinetics			
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
PI: B. Bunow Others: J. Kervenez		Expert Professor	LAS/DCRT Univ. of Tech. Compugne, France
A. Kaylan D. Mikulecky		Research Professor	DCCP, ICI Medical College of Virginia
R. Houdier R.L. Chragar A. Chrambach		Biochemist Mathematician Biochemist	LB, WILIE LAS, DCRT BR, WICHD
COOPERATING UNITS (if any) NONE			
LAB/BRANCH Laboratory of Applied Studies			
SECTION Applied Mathematics Section			
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205			
TOTAL MANPOWER 10		OTHER 10	
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER			
<input checked="" type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEW			
SUMMARY OF WORK (500 words or less - outline subjects) This project investigates the fundamental problems in biology: (1) the role of dynamic patterns in embryology and evolution, (2) the kinetics of enzymes located in cell membranes, (3) the kinetics of enzymes derived from malignant and normal cells in culture, (4) mathematical modeling of isoelectric focusing studies, (5) thermodynamics of biometric mechanisms in mitochondria, and (6) development of a new paradigm for biological modeling based upon topological representation and use of network modeling languages. Simulation on digital computers, particularly with network modeling languages, numerical solution of differential equations, and nonlinear regression analysis are the main tools in these investigations. While these problems are diverse in their biological background, they all share a common basis of mathematical and physical content through the role played by conservation laws and the mathematical methods involved in their resolution.			

PHS-6040
 (Rev. 2-61)

2. Simulation of O₂ Saturation of Hb involves four governing quantities (O₂ pressure, CO₂ pressure, pH, and 2,3-DPG concentration). An efficient model expression is required incorporating these quantities with a manageable number of parameters so that various types of Hb can be modeled. We are in the midst of designing both the validating experiments and the model.

- Cytochromes in Mitochondria

Richard W. Hendler (NHLBI); O.H. Setty (Visiting Associate); K.V. Subba Reddy (Visiting Fellow); Barry Bunow (AMS, DCRT).

1. An article on analysis of titration data by Single Value Decomposition techniques has just been published in *Analytical Biochemistry*.

2. A paper on this topic is being presented to a mathematical conference at the SIAM 30th Anniversary Meeting.

3. Work on the midpoint potential of *E. coli* cytochromes is now being extended to beef heart mitochondria and the other mammalian cells. By using a new rapid-scan spectrophotometer, we can now do kinetic studies as well as more reliable equilibrium studies.

4. A suspension of cells is given a pulse of O_2 . The uptake of O_2 and the production of H is monitored by computer, which must smooth the data and compensate for O_2 and H electrode delay times, in addition to several other monitoring functions. The program is running and producing good results.

5. In collaboration with B. Bunow, we are attempting to explain the oxidant-induced reduction of one of the b-cytochromes by developing a thermodynamically consistent model that also fits the observations.

- Phytic Acid Titration

William Evans (Agr. Res., New Orleans). An article on the titration of twelve H binding sites of phytic acid has appeared in *J. Am. Oil Chem. Soc.*

- SVD Kinetic Studies

Ray Tate (DCRT); Jim Osborne (NHLBI); Randy Kincaid (NHLBI). SVD is useful in resolving the spectra of individually titrating species in a mixture because the mathematical form of the titration is known. Likewise, the form of kinetic relaxation may also be known (e.g., sum of exponentials). Therefore, complete spectra gathered as a function of time may also be analysed by SVD. An initial set of data involving the association of Calmodulin and Ca using fluorescence and CD spectra is being prepared.

Proposed Course: The curve-fitting scaling procedures need more tests. Work continues on every aspect of the cytochrome problem. Some actual designs of Hb analyzers should be produced this year. The Hb-O₂ saturation model should be ready for use.

Publications:

Evans, W.J., McCourtney, E.J., and Shrager, R.I.: Titration Studies of Phytic Acid. *J. Am. Oil Chemists' Soc.* 59: 189-191, 1982.

Shrager, R.I., and Hendler, R.W.: Titration of Individual Components in a Mixture with Resolution of Difference Spectra, pK's, and Resox Transitions. *Anal. Chem.* 544: 1147-1152, 1982.

[illegible]

Numerical Approximation: Techniques for the Solution of Reaction-Diffusion Systems in Biology

A novel numerical method of lines, used to approximately solve partial differential equations governing models of reaction-diffusion systems in biology, has been developed and analyzed. The somewhat general program FEMOL 1, which implements the computational procedure, includes various user-oriented adaptive features. These features include automatic space and time mesh selections, which are made by the computer and are appropriate for the solution of any particular problem.

Progress in FY82: Various goals were achieved this past year in the investigation of numerical approximation techniques for the solution of reaction-diffusion systems in biology. The most significant of these fall into three categories:

- **Software Development**
A somewhat general and easy-to-use method of lines program, FEMOL1, was developed, implemented, and tested. FEMOL1 is presently applicable to systems of two nonlinearly coupled time-dependent reaction-diffusion equations in one space dimension. This program was designed primarily as a tool for use by laboratory researchers and other NIH scientists in parametric studies. Many

standard user-oriented 'black box' features available in much commercial software, such as automatic estimation and control of time discretization errors, are contained in the program. FEMOL1 also includes a posteriori estimates of space discretization errors and a novel adaptive procedure, in which space meshes are modified during a problem's solution by the computer in order to control the space discretization errors.

- **Application to Biological Models**
FEMOL1 was used in computational experiments to evaluate the effects of various numerical approximation parameters in the method of lines solution of equations governing models of the microcirculation, population ecology, and electrical impulse conduction in nerves. Such a study is important, in that the roles of biological parameters in models are often obscured by the effects of the specific approximation parameters used in computations. These experimental results form the basis of a future publication.

- **Development of Mathematical Theory**
Many new mathematical results were obtained concerning the effectiveness of the a posteriori estimators used in FEMOL1. This theory not only supports the computational procedures used, but also prescribes reliable and efficient means by which space discretization errors should be estimated and controlled in more general problems arising in practice and (as seen in the computational experiments) in cases where underlying mathematical assumptions break down. The contents of these results were included in two publications.

Proposed Course: Future investigations of numerical approximation techniques used in the study of biomathematical models will comprise (1) the extension of the capabilities of the method of lines program FEMOL1, and (2) the modification and implementation of other techniques and software that were developed previously in LAS and elsewhere for the solution of specific problems encountered by NIH researchers.

Publications:
Bieterman, M., and Babuska, I.: The Finite Element Method for Parabolic Equations. I. A Posteriori Error Estimation. *Numerische Mathematik* (in press).
Bieterman, M., and Babuska, I.: The Finite Element Method for Parabolic Equations. II. A Posteriori Error Estimation and Adaptive Approach. *Numerische Mathematik*. (in press).

MEMORANDUM (CHECK INFORMATION REQUESTED) PROJECT NUMBER (DO NOT USE THIS SPACE)		N.I.H. DEPARTMENT OF HEALTH AND HUMAN SERVICES OFFICE OF SERVICES INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 301 CT00045-04 LAS	
PERIOD COVERED October 1, 1981 to September 30, 1982 TITLE OF PROJECT (40 characters or less) Numerical Approximation Techniques for the Solution of Reaction-Diffusion Systems in Biology					
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: A. Babuska OTHERS: J.S. Fletcher Chief, AMS P. Bunow Biostatistician, AMS I. Babuska Professor, I.P.S.T. LAS DCBT LAS DCBT Univ. of MD					
COOPERATING UNITS (if any) none					
LABORATORY Laboratory of Applied Studies					
SECTION Applied Mathematics Section					
INSTITUT AND LOCATION DCBT, B1H, Bethesda, MD 20205					
TOTAL MANHOURS 0.8		PROFESSIONAL 0.8		GROUP	
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER					
<input checked="" type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEWS (NUMBER OF WORK DAYS WORK OR LESS - SPECIFY IN COMMENTS) A novel numerical method of lines, used to approximately solve partial differential equations governing models of reaction-diffusion systems in biology, has been developed and analyzed. The somewhat general program FEMOL 1, which implements the computational procedure, includes various user-oriented adaptive features. These features include automatic space and time mesh selections, which are made by the computer and are appropriate for the solution of any particular problem.					

Monitoring of the CNS in Critically Ill Patients

This new project is a joint effort between the Laboratory of Applied Studies and the Department of Critical Care Medicine to design, build, and implement a highly clinically oriented, distributed-processing, microcomputer-based system for analysis and display of scalp-recorded neuroelectric signals. As a part of the total noninvasive monitoring effort, this tool will then be used to investigate the degree of dysfunction in neurologically impaired patients, correlate the indices developed with other measures of cerebral function, and evaluate the effectiveness of various therapeutic interventions.

Background and Objectives: In the critically ill medical patient with multiple organ dysfunction, impaired brain function frequently coincides with deterioration of other major systems. However, the degree of damage and capacity for restoration of the brain does not necessarily parallel that of the rest of the body. In addition, assessment of the central nervous system is hampered by limitations imposed by procedures (e.g., endotracheal intubation) and/or drugs (e.g., Pavulon).

INTERCOM-SCIENCE INFORMATION (ADVANCE) PROJECT NUMBER (DO NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INSTRUMENTAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00099H-01 LAS
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (80 characters or less) Monitoring of the CNS in Critically Ill Patients		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI:	A.C. Burgess	Senior Staff Fellow SAC: ROFT
OTHERS:	J. Perillo	Chief CC CC
	C. Robinson	Senior Investigator CC CC
	M.W. Horton	Computer Systems Analyst LAS DORT
	E.W. Pottala	Electronics Engineer LAS DORT
	J.J. Bailey	Chief, M&I LAS DORT
COORDINATING UNIT (if any) Critical Care Medicine Department, CC		
LABORATORY Laboratory of Applied Studies		
SECTION Medical Applications Section		
PROJECT LOCATION CASA, NID, Bethesda, MD 20205		
TOTAL MANPOWER:	PROFESSIONAL:	OTHER:
CHECK APPROPRIATE BOXES		
<input type="checkbox"/> (a) HUMAN SUBJECTS	<input type="checkbox"/> (b) HUMAN TISSUES	<input type="checkbox"/> (c) NUCLEAR
<input type="checkbox"/> (d) MINDS	<input type="checkbox"/> (e) INTERVIEW	
SUMMARY OF WORK (200 words or less - underline keywords)		
<p>This new project is a joint effort between the Laboratory of Applied Studies and the Department of Critical Care Medicine to design, build, and implement a highly clinically oriented, distributed-processing, microcomputer-based system for analysis and display of scalp-recorded neuroelectric signals. As a part of the total noninvasive monitoring effort, this tool will then be used to investigate the degree of dysfunction in neurologically impaired patients, correlate the indices developed with other measures of cerebral function, and evaluate the effectiveness of various therapeutic interventions.</p>		

PH-5040
(Rev. 2-78)

The most frequently employed tool for evaluation of the central nervous system, the neurological exam, suffers from its discontinuous and subjective nature and is highly dependent upon the examiner's skill. Many investigators have attempted to apply various diagnostic and monitoring techniques to the problem of assessing the neurological status of the critical care patient.

Past efforts have been hindered by equipment artifacts and have required a high degree of skill on the part of the technician and the interpreter. This project will overcome the great difficulty of undertaking detailed microvolt-level signal analysis through the innovative use of state-of-the-art technology and multidisciplinary approach.

Progress during FY82: A detailed literature search and exhaustive commercial product evaluation has been carried out. Dr. Burgess attended the state-of-the-art Evoked Potential course at Duke University. System requirements have been determined, instrumentation design has been completed, and equipment purchases have been initiated.

Significance: Apart from the technological task of demonstrating a system that will reliably and semi-automatically obtain and process data from MICU patients, we seek answers to the following questions:

1. Which electrophysiological parameters can be used to best follow the functional neurologic status of the patients?
2. What is the optimal protocol for obtaining data in order to balance recording requirements and nursing care needs?
3. How can the parameters be best combined into a meaningful profile and be best displayed to provide comprehensive yet easy-to-assimilate clinical information?
4. How does the information offered by this system compare to other neurodiagnostic techniques?
5. How does this system improve our overall care of the patient and our understanding of the pathophysiological dynamics?

Proposed Course: The completed system will include: (1) a precision analog front-end with high noise immunity for detection, amplification, and filtering of the spontaneous and evoked EEG activity; (2) stimulators for delivery of visual, auditory, and somatosensory stimuli; (3) a central processor with intelligent peripherals for data acquisition, manipulation, calculation, and storage; and (4) a display capable of high resolution graphics and printout for presentation of current and past data, trends, and interpretive imaging.

Extensive development of both hardware and software will be carried out during the coming year. Instrumentation to be built includes a CPU interfaced preamplifier/filter and a computer control for the stimulators. A hardware as well as a software interface for an array processor will have to be developed. Programs will enable simultaneous stimulation, data acquisition, storage, and display. Operating in the realtime environment and employing an array processor for rapid computation will require complex and flexible data handling routines.

Publications:

Burgess, R.C.: An instrument to add evoked potential capability to the standard electroencephalograph. *EEG and Clin. Neurophysiol.* 53: 33, 1981.

Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease

This project--through a collaborative effort of LAS with the Nuclear Medicine Department, CC and the Clinical Hematology and Pulmonary Branches, NHLBI--is directed toward a deeper understanding of pulmonary pathophysiology through the construction of computer-based models of pulmonary gas exchange and respiratory mechanics and through comparisons of model predictions with real patient data.

Progress in FY82: The system designed, specified, and purchased during FY81 for breath-by-breath analysis of pulmonary gas exchange has been assembled. Interfaces for the bicycle ergometer and treadmill controllers to enable online computer control and data acquisition were designed and built. Necessary support equipment, such as an expired gas cooler and an analog tape deck controller, were fabricated. LAS has been developing software to effectuate realtime exercise testing and has been performing calibration of the individual instruments as well as the integrated system.

Proposed Course: Preliminary testing of the new system on volunteer subjects is just beginning and substantial additional data will be collected for both system validation and establishment of a baseline data base. Numerous studies of the gas transport system are possible. An experimental protocol to evaluate the use of Hydralazine in sickle cell disease in collaboration with the NHLBI Hematology Branch has been approved. Studies of cardiorespiratory ability in both patients and athletes are in the planning stages in collaboration with the NHLBI Pulmonary Branch.

Publications: None.

WITHHOLDING SOURCE INFORMATION (MANDATORY) PROJECT NUMBER (DO NOT use this space)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NCI/CCO INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER D01 OT00054-06 LAS	
PERIOD COVERED October 1, 1981 to September 30, 1982					
TITLE OF PROJECT (30 characters or less) Computer-based Studies in Pulmonary Pathophysiology and Respiratory Disease					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
PI:		R.C. Burgess		Senior Staff Fellow LAS DCRT	
OTHERS:		A.W. Hienhaus		Chief CHB NHLBI	
		R.G. Crystal		Chief PH NHLBI	
		M.R. Horton		Computer Systems Analyst LAS DCRT	
		E.W. Pottala		Electronics Engineer LAS DCRT	
		J.L. Bailey		Chief, MAS LAS DCRT	
		E.K. Harris		Chief LAS DCRT	
COOPERATING UNIT (if any) Clinical Hematology, Pulmonary Branch, NHLBI, Nuclear Medicine Dept., CC Branch, NHLBI					
LABORATORY Laboratory of Applied Studies					
SECTION Medical Applications Section					
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205					
TOTAL MANPOWER		PROFESSIONAL		OTHER	
2.0		2.0			
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER					
<input checked="" type="checkbox"/> (d) MURINE <input type="checkbox"/> (e) INTERVIEWS					
SUMMARY OF WORK (500 words or less - underline key words) This project--through a collaborative effort of LAS with the Nuclear Medicine Department, CC and the Clinical Hematology and Pulmonary Branches, NHLBI--is directed toward a deeper understanding of pulmonary pathophysiology through the construction of computer-based models of pulmonary gas exchange and respiratory mechanics and through comparisons of model predictions with real patient data.					

FORM 460
(Rev. 7-81)

Investigation of Hybrid Computing for the Construction of Simulation Models and for the Analysis of Physiologic Signals

This project was undertaken to develop physiologic simulation models using hybrid computing and also to use hybrid computing techniques to analyze physiologic signals such as electrocardiogram, electroencephalogram, and electromyogram.

Progress During FY82: The study of neural signals in the rat (hippocampus and sensory cortex) has been deferred by that investigator and only recently re-initiated.

The Division of Cardio-Renal Drug Products, FDA, is investigating the early detection of cardiac toxicity resulting from drug therapy. Rat electrocardiograms are being used to determine the sensitivity of detection. The data has been redigitized and reformatted so that it can be analyzed by an automatic vector cardiographic program acquired by LAS several years ago.

Two simulation languages, NET2 and SPICE2, have been implemented on NIH computer systems. Both languages are available on the IBM System 370, and SPICE2 is also available on the VAX computer

belonging to the Technical Development Section, NIMH. The single retinal cone cell model has been used to verify the above systems; a manuscript is in preparation.

Proposed Course: The MAC-16 system will have continued use for ECG processing from the Framingham Heart Study (see project report on electrocardiography).

Analysis of FDA data on rat electrocardiograms will continue in FY83.

Network simulation studies will continue with the development and implementation of additional physiologic models using SPICE2 and NET2.

Publications and Abstracts: None.

Computer Systems for Nuclear Medicine

This project involves computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Nuclear Medicine Department of the Clinical Center and in collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiology and myocardial perfusion scintigraphy, renal dynamics, and pulmonary ventilation-perfusion relationships.

Progress during FY82:

- Renal Scintigraphy
- The results of preliminary work carried out in FY76-FY80 have been published in several journals. These studies demonstrated significant enhancement of routine renography using functional mapping techniques. After a technical development and software upgrading effort was accomplished in FY81, definitive evaluation of the technique was carried out in nine dogs. Contrast angiography, routine radionuclide renography, and functional renal mapping were performed before, one month after, and 12 months after unilateral renal artery ligation. Histopathological study of kidneys removed from the sacrificed dogs is now underway. A manuscript correlating the pathological findings with the functional maps is in preparation.

- Cardiac Scintigraphy
- In collaboration with Nuclear Medicine and the Cardiology Branch, LAS has begun investigation of several parameters reflecting mobility of the heart wall including ejection fraction, regional emptying time, phase (of first Fourier harmonic), and maximum ejection rate. Programs have been written to compute these parameters globally or for any sectors of the heart image. The test data base

CHIEF/PROJECT/LEADER INFORMATION (CHANGE) PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF HEALTH	PROJECT NUMBER 201 C000004-11 LAS
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (50 characters or less) Investigation of Hybrid Computing for the Construction of Simulation Models and for the Analysis of Physiologic Signals		
NAME, LAST/INITIALS AND (FEDERAL AFFILIATIONS) AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PERSONNEL (PERSONNEL) LOCATED ON THE PROJECT P.I. G.W. Pottala Elec. Engineer LAS DOW		
OTHERS: J.J. Bailey Chief, NIS LAS DOW B. Sumner Expert LAS DOW W.C. Van Arsdale Pharmacologist DDB FDA M. De Nyck Visiting Scientist LS NINCDS		
COOPERATING UNIT (S) (4+) Laboratory of Neurotoxicology, NINCDS Division Cardio-Renal Drug Products, FDA		
LAB/BRANCH Laboratory of Applied Studies		
SECTION Medical Applications Section		
INSTITUT AND LOCATION DOW, W.D., Delaware, MD 20705		
TOTAL MANPOWER 1-1 PROFESSIONAL 1-0 OTHER 0-1		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NESTING <input type="checkbox"/> (d) MURINE <input type="checkbox"/> (e) INTERVIEW		
SUMMARY OF WORK (100 words or less - underline keywords) This project was undertaken to develop physiologic simulation models using hybrid computing and also to use hybrid computing techniques to analyze physiologic signals such as electrocardiogram, electroencephalogram, and electromyogram.		

includes rest and exercise studies on 40 normal volunteers, 24 patients with coronary disease and known resting apical abnormalities (hypokinesis, akinesis, or dyskinesis), and 15 patients with cardiomyopathy.

- Image Processing

Signal-to-noise (S/N) ratio and Fourier harmonic content of global and regional time-activity curves (TACs) were thoroughly studied in this data base. These studies showed that the physiological signal is largely contained in four or fewer harmonics and that higher harmonics probably represent noise relating to the counting statistics of the TAC. They further showed that smaller regions have relatively higher noise and that regions smaller than 1/4 of the ventricular region-of-interest produce higher proportions of TACs that cannot be distinguished from background TACs in terms of S/N ratio or harmonic content. Hence, regional parameters extracted from such TACs are unreliable. Finally, these studies showed that global ejection fraction is a good classifier of normal and abnormal cases but regional ejection fraction does not appear to be additionally helpful in separating apical abnormalities (related to coronary artery disease) from diffuse abnormalities (related to cardiomyopathy). However, regional emptying time (time to the minimum of the TAC) does appear to separate apical from diffuse abnormalities. A series of manuscripts describing these studies is in preparation.

Proposed Course:

- Renal Scintigraphy

Further evaluation and refinement of the functional mapping technique is planned utilizing alternative renal lesions in canine subjects. Limitations as well as advantages of functional mapping in pathophysiology of various etiologies will be explored.

- Cardiac Scintigraphy

A statistical analysis of the data base will be pursued, one possible outcome of which might be a discriminant function with various parameters to achieve optimal separation of normals from abnormals. Another interesting study will involve those patients with myopathy secondary to adriamycin therapy, using each patient before therapy as his own control. Other patients who have normal contractility at rest but abnormalities upon exercise form an additional interesting data base.

- Image Processing

When the expanded DeAnza system together with magnetic tape and disk drives are operational, it will facilitate study of paired myocardial (Thallium) and blood pool image sequences. Refined edge detection, assessment of wall motion abnormalities and perfusion, and more accurate determination of volumes are planned.

A model to demonstrate the effect of known amounts of additive noise on the detectability of regional wall motion abnormalities is planned.

Publications: None.

Computer-Aided Analysis of Electrocardiograms

These studies, continuing since 1970, have been directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer systems for analysis of routine electrocardiograms

INSTITUTION (PLEASE INDICATE INFORMATION EXCHANGE PROJECT NUMBER (ON NOT USE THIS SPACE))		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL CENTER FOR HUMAN RESEARCH PROJECT	PROJECT NUMBER 001 CT00005-11 LAS
PERIOD COVERED October 1, 1961 to September 30, 1962			
TITLE OF PROJECT (in characters or less) Computer Systems for Nuclear Medicine			
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PERSONNEL PERSONNEL ENGAGED ON THE PROJECT S.L. Bacharach Physician NM CC OTHERS: R.O. Brown Clinical Associate CB KHLBI J.J. Bailey Chief, Med. Appl. Sec. LAS DCMT R.C. Burgess Senior Staff Fellow LAS DCMT H.A. Douglas Comp. Syst. Analyst LAS DCMT P.P. van Rijk Visiting Scientist LAS DCMT M.V. Green Ch. Appl. Physics Sec. NM CC A.S. Jones Chief, Diagnostic Imaging NM CC H.G. Ostrow Engineer CSL DCMT			
COOPERATING UNITS (if any) Nuclear Medicine Department, CC, NIM Computer Systems Laboratory, DCEB, NIM			
LABORATORY Laboratory of Applied Studies			
SECTION Medical Applications Section			
INSTITUTE AND LOCATION DCMT, NIM, Bethesda, MD 20205			
TOTAL MANUSCRIPTS 3.1		OTHERS 0.1	
CHECK APPROPRIATE BOX(ES) <input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER			
(1) (a) MINOR (2) (a) INTERVIEW SUMMARY OF WORK (500 words or less - underline keyphrases) This project involves computer-based mathematical analysis, pattern recognition, and image processing in support diagnostic activities in the Nuclear Medicine Department of the Clinical Center and collaborating Institutes. Applications include computerized SCL-gated radionuclide angiography and myocardial perfusion scintigraphy, renal dynamics, and pulmonary ventilation-perfusion relationships.			

(ECG's). Further studies will involve new methods of feature extraction and design of criteria by computer techniques and their use in epidemiological studies.

Progress during FY82: A set of ECGs was recorded on four different occasions on each of four staff members of the Framingham Heart Project. One ECG from each member was digitized at 1000 samples/sec and the others at 250 samples/sec. From these data the analytic variation, within person variation, and group biological variation were estimated and compared with similar studies done by Simonson in 1949. A manuscript is in preparation.

Proposed Course: Georgetown University Medical Center has acquired 12 simultaneous lead ECGs on a group of patients with documented cardiac disease. GUMC has proposed a collaborative project with LAS to evaluate three of the better-known programs using this data base.

Meanwhile, LAS continues to study the epidemiologic significance of the routine ECG in collaboration with the investigators of the Framingham Heart Study. The ECG correlates of such heart diseases as coronary disease, mitral prolapse, and asymmetric septal hypertrophy in a free-living population are of particular interest.

Publications and Abstracts:

Bailey J.J., Berson, A.S., Jackson, L.K., Milliken, J.A., Stevens, J.M., Tolan, G.D., and Wolf, H.K.: Evaluation Methodologies for ECG diagnostic systems. In Bonner, R.E., and Pryor, T.A. (Eds.): *Computerized Interpretation of the ECG VI*. New York, Engineering Foundation, 1981 (in press).

Macfarlane, P.W., Chen, C.Y., and Bailey, J.J.: A comparison of point scoring techniques for the diagnosis of LVH. In Macfarlane, P.W. (Ed.): *New Frontiers in Electrocardiology*. New York, John Wiley & Sons, 1981 (in press).

Computer-based studies in ultrasonography

This project involves collaboration between LAS and the Cardiology Branch, NHLBI. It is directed toward computer-based processing for image enhancement, pattern recognition, and three-dimensional reconstruction from ultrasound data. Wide-angle, phased array echocardiography is the principal source of data.

Progress in FY81: Resolution of hardware and software defects in the upgraded DeAnza image processing system has forced deferral of further work on this project (see project on Computer Based Analysis and Image Processing in Electron Microscopy).

Publications and Abstracts: None.

INTERDISCIPLINARY SCIENCE INFORMATION (EXCHANGE) PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NHLBI INTRANSMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00002-12 LAS
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (20 characters or less) Computer-Aided Analysis of Electrocardiogram		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENAGED ON THE PROJECT		
PI: J.J. Bailey Chief, M&S LAS DORT		
OTHERS: S.A. Harris Chief LAS DORT M.R. Horton Computer Systems Analyst LAS DORT D. Savage Framingham Heart Study NHLBI		
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Applied Studies		
DIVISION Medical Applications Section		
INSTITUTE AND LOCATION DCU, NIN, Bethesda, MD 20205		
TOTAL MANPOWER 1.3 PROFESSIONAL 3.2 OTHER 0.1		
CHECK APPROPRIATE BOXES: (a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER		
(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER		
CHECK IF WORTHY (a) INTERVIEW (b) INTERVIEW		
SUMMARY OF WORK (200 words or less - underline keywords) These studies, continuing since 1970, have been directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer systems for analysis of routine electrocardiograms (ECGs). Further studies will involve new methods of feature extraction and design of criteria by computer techniques and their use in epidemiological studies.		

PG-0040
(Rev. 2-81)

INTERDISCIPLINARY SCIENCE INFORMATION (EXCHANGE) PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NHLBI INTRANSMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT000045-04 LAS
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (20 characters or less) Computer-based studies in ultrasonography		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENAGED ON THE PROJECT		
PI: S.W. Pottlitz LAS DORT		
OTHERS: M.A. Douglas LAS DORT B.J. Macdon CR NBLBI J.J. Bailey LAS DORT		
COOPERATING UNITS (if any) Cardiology Branch, NBLBI		
LAB/BRANCH Laboratory of Applied Studies		
DIVISION Medical Applications Section		
INSTITUTE AND LOCATION DCU, NIN, Bethesda, MD 20205		
TOTAL MANPOWER 0.4 PROFESSIONAL 0.2 OTHER 0.2		
CHECK APPROPRIATE BOXES: (a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER		
(a) HUMAN SUBJECTS (b) HUMAN TISSUES (c) NEITHER		
CHECK IF WORTHY (a) INTERVIEW (b) INTERVIEW		
SUMMARY OF WORK (200 words or less - underline keywords) This project involves collaboration of LAS, with the Cardiology Branch, NBLBI. It is directed toward computer-based processing for image enhancement, pattern recognition, and three-dimensional reconstruction from ultrasound data. The principal sources of data are wide-angle, phased array echocardiography.		

PG-0040
(Rev. 2-81)

Computer Based Analysis and Image Processing in Electron Microscopy and X-ray and Electron-Loss Spectroscopy

This project involves collaboration of LAS with several NIH Institutes. It is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally x-rays and electron energy loss spectra, derived from biological specimens studied in an analytical electron microscope.

Progress During FY82: The DeAnza image processing system has been upgraded from a maximum image size of 256 by 256 pixels to a maximum of 512 by 480 pixels. Testing of this upgraded system revealed many serious hardware defects. The vendor has spent most of FY82 resolving these problems. The same vendor provided the hardware interface between the DeAnza system and the magnetic tape and disk drives. This interface has also been sent back to the vendor for correction. Consequently many projects depending upon this system have been delayed (see Ultrasound and Nuclear Medicine).

Statistical analyses currently are being performed to determine the sample size necessary to detect reliably changes in density of dense bodies in digitally acquired electron micrographs of platelets.

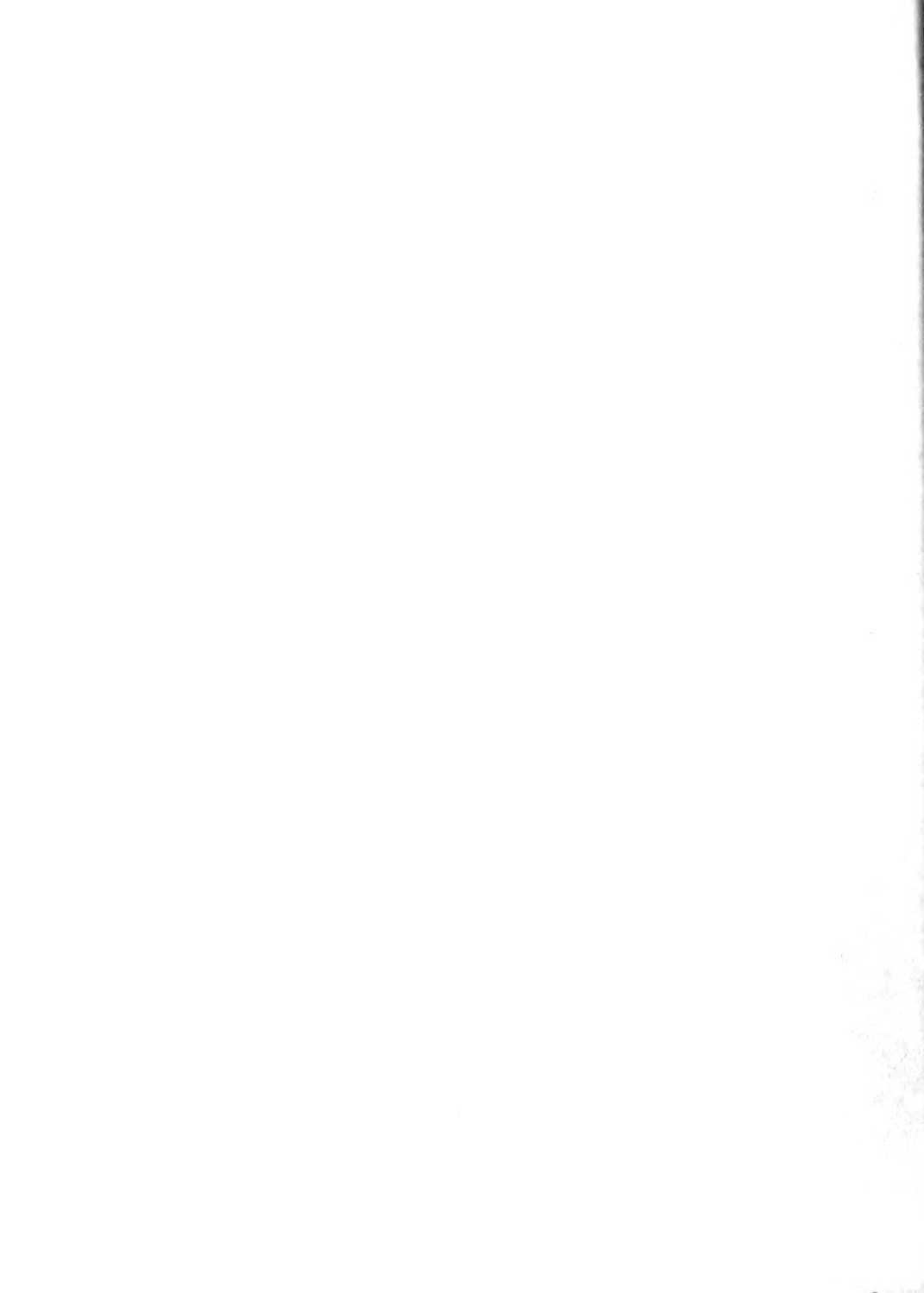
Proposed Course: The study of the basic physics and the formulation of appropriate mathematical/statistical models needed to achieve the analytical capabilities will require extensive work with phantoms, i.e., specimens of known composition that are very thin, prepared by such means as vacuum evaporation. There will need to be extensive studies of the signal/noise ratio in phantoms and in biological specimens. Potential problems with contamination and with specimen destruction by the high energy beam also need to be studied. Sophisticated algorithms for element recognition and location, image enhancement, etc., need to be designed.

LAS proposes to undertake some of these objectives in collaboration with participating wet laboratories. The DeAnza system has been upgraded from a maximum image size of 256 x 256 pixels to 512 x 480 pixels. Images acquired at Brookhaven are 512 x 512 pixels; when the expanded system with the new magnetic tape and disk drives is operational, it will allow more rapid processing of the images obviating the need for data compression or partitioning.

Publications and Abstracts: None.

ORGANIZATION: SCIENCE INFORMATION EXCHANGE PROJECT NUMBER: [] AND [] AND [] AND []		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH NOTICES TO INDUSTRY RESEARCH PROJECT		PROJECT NUMBER D01 CT00042-04 LAS	
PERIOD COVERED October 1, 1981 to September 30, 1982					
TITLE OF PROJECT (60 characters or less) Computer Based Analysis and Image Processing in Electron Microscopy and X-ray and Electron-Loss Spectroscopy					
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
P.I. H.A. Douglas Computer Systems Analyst LAS DCRT					
OTHERS: S.V. Pottala Elec. Eng. CSL DCRT J.L. Costa Medical Officer CV BEHE J.J. Bailey Chief, NAS LAS DCRT					
COOPERATING UNITS (if any) Clinical Neuropharmacology, NINDS, Laboratory of Chemistry, NIDDK.					
LAB/BRANCH Laboratory of Applied Studies					
SECTION Medical Applications Section					
INVESTMENT AND LOCATION DCRT, HHS, Bethesda, MD 20205					
TOTAL MATERIALS: PROFESSIONAL: OTHER: 2.0 1.1					
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (1) HUMAN SUBJECTS <input type="checkbox"/> (4) HUMAN TISSUES <input type="checkbox"/> (6) NEITHER <input type="checkbox"/> (11) MINDS <input type="checkbox"/> (12) INTERVIEWS					
SUMMARY OF WORK (200 words or less - underline keywords) This project involves collaboration of LAS and several NIH Institutes. It is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally x-rays and electron energy loss spectra derived from biological specimens studied in an analytical electron microscope.					

7-10-82
 (Rev. 2-81)



Physical Sciences Laboratory

George H. Weiss, Chief

Summary of Activities

Consulting Services. R. A. Brooks (SN, NINCDS); J. Shapiro (CC, DIR); A. Pikus (CC, OPD); J. D. Dillon (Walter Reed Medical Center); B. Sonies, M. Stone (CC, REHAB); L. Nadel (CSL, DCRT); G. Knott (LSM, DCRT); H. Edelhoch (CE, NIADDK). Members of PSL collaborate with and advise researchers at NIH in several areas of applied mathematics and applied physics.

A study on the lifespans of German veterans who sustained head injuries in World War I has been completed. A comparison of data on these veterans and on uninjured veterans showed that the lifespans were little affected by injuries until approximately the age of 60, after which death rates in the injured group exceeded those in the control group. Further, the only reliable prognostic factor for the occurrence of early death was posttraumatic epilepsy, while other measures of severity of injury showed no predictive value.

A theory that enables one to calculate the statistical errors in parameters estimated from positron emission tomography data has been developed. The validation of this theory by simulation will be undertaken and then application to the data of Dr. Rodney Brooks will be made.

A joint effort with members of the Speech Rehabilitation Department of the Clinical Center and with Dr. Lawrence Nadel of the Computer Systems Lab has begun on the use and quantitation of ultrasonic imaging to the study of tongue configuration in speech. So far the ultrasonic images have been digitized, and various studies completed on the reliability of measurements processed in this way.

Studies in Mathematics and Statistics. George H. Weiss (PSL). A meeting on random walks and their application to the physical and biological sciences was held at the National Bureau of Standards on June 28-July 1, with participants from around the

world. PSL has worked on several applications of random walk theory to physical problems. One is the configuration of polymer chains near surfaces, and another is a problem derived from crystallography. A second project that has been completed relates to order statistics of diffusion processes that may or may not be spatially homogeneous.

Several statistical tests for examining the relatedness of DNA sequences from different species have been developed. Heretofore, tests of relatedness were produced by simulation only; our tests, while not comprehensive, are nevertheless exact.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph J. Nossal (PSL). Studies have been completed on changes in mechanical properties occurring near the gel-sol transition in polymer gels. A theory is being developed to relate macroscopic measured parameters to the underlying microscopic structure of the gel. The techniques that have been developed in this project are currently being used to investigate properties of gels formed from glycoproteins and of clots formed from reconstituted human plasma.

Two-dimensional Fourier Transform Nuclear Magnetic Resonance Spectroscopy. James A. Ferretti (PSL). Considerable progress has been made in applying two-dimensional NMR spectroscopy to the measurement of rate constants in enzyme reactions. In principle it has been shown that one can monitor all of the pathways in a complex exchanging system.

Theory and Measurement of Intermolecular Forces. Adrian Parsegian (PSL). For the first time ever, measurements of the forces between molecules have been made using a combination of thermodynamics and crystallographic methods. In particular these measurements have been made for the repulsive forces between parallel DNA double helices.

Quantitative Analysis of Cell Electronmicroscopy and Plasma Membranes. Nahum Gershon (PSL). This project uses image processing techniques to interpret electronmicrograph pictures. Measurements have been made of the volume, surface area, and pore size of the cytoskeleton of cells. These measurements show that the cytoskeleton occupies a small volume of the cytoplasm contrary to what is usually assumed. A computer system is being assembled to study three-dimensional cell structure.

Research Projects

Consulting Services

Consulting services are provided to NIH researchers on problems requiring knowledge of advanced techniques in applied mathematics, physics, and statistics. Projects have been completed relating to interpolation errors in computerized tomography, to the occurrence of audiologic defects in patients and relatives of patients having osteogenesis imperfecta, on the consequences of head injuries for life span, and on the occurrence and time course of posttraumatic epilepsy.

A project has been started on the estimation of errors in parameters measured by positron emission tomography, and a theory has been developed to estimate expected errors from the data. Another project with the Clinical Center is on the use of ultrasonic measurements to characterize tongue position in speech. The biochemical characterization of coated and uncoated vesicles by a combination of ultracentrifugal techniques and light scattering is another project recently initiated.

Publications:

- Rish, B. L., Caveness, W. L., Dillon, J. D., Kistler, J. P., Mohr, J. P., and Weiss, G. H.: Analysis of brain abscess following penetrating craniocerebral injuries in Vietnam. *Neurosurgery* 9:535-541, 1981.
- Shapiro, J. R., Pikus, A., Weiss, G. H., and Rowe, D. W.: Hearing and middle ear function in osteogenesis imperfecta. *J. Am. Med. Assoc.* 247:2120-2126, 1982.
- Weiss, G. H., Caveness, W. F., Einsiedel-Lechtape, H., and McNeel, M. L.: Life expectancy and causes of death in a group of head injured veterans. *Arch. Neurol.* (in press).
- Weiss, G. H., Feeney, D. M., Caveness, W. F., Dillon, J. D., Kistler, J. P., Mohr, J. P., and Rish, B. L.: Prognostic factors for the occurrence of posttraumatic epilepsy. *Arch. Neurol.* (in press).
- Weiss, G. H., and Rice, J. A combinatorial problem in pharmacology. *J. Math. Biol.* (in press).
- Weiss, G. H., Talbert, A., and Brooks, R. A.: The use of phantom views to reduce CT streaks due to insufficient sampling. *Phys. in Biol. and Med.* (in press).

INFORMATION SERVICE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT USE THIS SPACE)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE OFFICE OF INTRAMURAL RESEARCH PROJECTS	PROJECT NUMBER Z01 CT 00022-15 PSL
PERIOD COVERED October 1, 1981 to September 30, 1982			
TITLE OF PROJECT (in characters or less) Consulting Services			
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED IN THE PROJECT PI: George H. Weiss, Chief, PSL, DCRT Other: James E. Kiefer, PSL, DCRT Ralph Nossal, Ph. D., PSL, DCRT			
COOPERATING UNITS (if any) R. A. Brooks, SN, NINCDS; J. Shapiro, CC, DIR; A. Pikus, CC, OPO; J. B. Dillon, Walter Reed Medical Center; B. Somes, CC, RENAR; M. Somes, CC, RENAR; L. Nadel, CSE, DCRT; G. Knott, LSH, DCRT; W. Edelbrock, CC, NIAID; L. Nadel, CC, DCRT			
PHYSICAL SCIENCE LABORATORY SECTION			
INSTITUTE AND LOCATION Division of Computer Research & Technology			
TOTAL MANPOWER 1.0		PROFESSIONAL 0.5	
OTHER 0.1			
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN ISSUES <input type="checkbox"/> (c) BILITEN			
<input checked="" type="checkbox"/> (a) MINDS <input type="checkbox"/> (a2) INTERVIEWS			
SUMMARY OF WORK (500 words or less - include the key words) Consulting services are provided to NIH researchers on problem requiring knowledge of advanced techniques in applied mathematics, physics, and statistics. Projects have been completed relating to interpolation errors in computerized tomography, to the occurrence of audiologic defects in patients and relatives of patients having osteogenesis imperfecta, on the consequences of head injuries for life span, and on the occurrence and time course of posttraumatic epilepsy. A project has been started on the estimation of errors in parameters measured by positron emission tomography, and a theory has been developed to estimate expected errors from the data. Another project with the Clinical Center is on the use of ultrasonic measurements to characterize tongue position in speech. The biochemical characterization of coated and uncoated vesicles by a combination of ultracentrifugal techniques and light scattering is another project recently initiated.			

PHS-6040
(Rev. 2-61)

Studies in Mathematics and Statistics

A comprehensive review article on random walks and their application in chemical physics and biology has been completed. Arrangements for an international meeting on random walks and their applications, sponsored by NIH and NBS were made, and the meeting was held from June 28 to July 1, 1982. Several statistical tests have been developed for measuring the relatedness of DNA sequences from different species. A study of first passage problems for diffusion processes with spatially inhomogeneous transition coefficients has been completed.

Publications:

- Kiefer, J. E., and Weiss, G. H.: A comparison of two methods for accelerating the convergence of Fourier series. *Comp. and Math.* 7:327-336, 1981.
- Rubin, R. J., and Weiss, G. H.: Random walks on lattices: The problem of visits to a set of points revisited. *J. Math. Phys.* 23:250-253, 1982.
- Weiss, G. H.: Random walks and their applications. *Amer. Sci.* (in press).
- Weiss, G. H., and Rubin, R. J.: Random walks: Theory and selected applications. *Adv. Chem. Phys.* (in press).
- Weiss, G. H., and Shlesinger, M. F.: On the expected number of distinct points in a subset visited by an N-step random walk. *J. Stat. Phys.* 27:355-363, 1982.

INTERAGENCY SERVICE FOR UNIVERSITY RESEARCH PROJECT NUMBER (DO NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00024-07 PSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (40 characters or less) Studies in Mathematics and Statistics		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATOR AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: George H. Weiss, Chief, PSL, DKRT Other: J. E. Kiefer, PSL, DKRT		
COOPERATING INSTITUTES (40 x 70) J. Rubin, Ph. D., Senior Scientist, NBS; K. E. Shuler, Ph. D., Univ. of California-San Diego; K. Lindenberg, Ph. D., Univ. of California-San Diego; B. West, La Jolla Institute		
LABORATORY Physical Sciences Laboratory SECTION		
INSTITUTE AND LOCATION Division of Computer Research and Technology TOTAL MANPOWER 0.8 PROFESSIONAL 0.5 OTHER 0.3		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a) WINDS <input type="checkbox"/> (a2) INTERVIEW SUMMARY OF WORK (200 words or less - underline keywords) A comprehensive review article on random walks and their application in chemical physics and biology has been completed. Arrangements for an international meeting on random walks and their applications, sponsored by NIH and NBS were made, and the meeting was held from June 28 to July 1, 1982. Several statistical tests have been developed for measuring the relatedness of DNA sequences from different species. A study of first passage problems for diffusion processes with spatially inhomogeneous transition coefficients has been completed.		

PHS-5040
(Rev. 2-78)

Theory of Biochemical Separation Techniques

The techniques of applied mathematics and statistics are applied to the design and analysis of biochemical experiments.

Several methods have been compared for estimating peak height and half-width of chromatographic peaks. These have led to a clear choice among methods currently being used. A similar investigation has been undertaken on Lorentzian peaks that arise in NMR measurements. A theory of kinetic tailing in chromatography has been developed using techniques devised for the study of hopping conduction in solids.

Publications:

- Weiss, G. H.: Optimal parameters for the measurement of the half-width of a Gaussian peak. *Sep. Sci. & Tech.* (in press).

INTERAGENCY SERVICE FOR UNIVERSITY RESEARCH PROJECT NUMBER (DO NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00014-15 PSL
PERIOD COVERED October 1, 1981 to September 30, 1982		
TITLE OF PROJECT (40 characters or less) Theory of Biochemical Separation Techniques		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATOR AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: George H. Weiss, Chief, PSL, DKRT		
COOPERATING INSTITUTES (40 x 70) John Rice, Professor of Statistics, University of California-San Diego		
LABORATORY Physical Sciences Laboratory SECTION		
INSTITUTE AND LOCATION Division of Computer Research and Technology TOTAL MANPOWER 0.1 PROFESSIONAL 0.1 OTHER 0.0		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (a) WINDS <input type="checkbox"/> (a2) INTERVIEW SUMMARY OF WORK (200 words or less - underline keywords) The techniques of applied mathematics and statistics are applied to the design and analysis of biochemical experiments. Several methods have been compared for estimating peak height and half-width of chromatographic peaks. These have led to a clear choice among methods currently being used. A similar investigation has been undertaken on Lorentzian peaks that arise in NMR measurements. A theory of kinetic tailing in chromatography has been developed using techniques devised for the study of hopping conduction in solids.		

PHS-5040
(Rev. 2-78)

Correlation Function Spectroscopy/Laser Light Scattering

Methods have been developed that utilize dynamic light scattering techniques to probe the mechanical rigidity and internal viscosity of polymer gels. Recent emphasis has been on characterizing changes in mechanical properties that occur near the gel-sol transition, as crosslink density and polymer concentrations are varied. The influence of solvent viscosity on the dissipation of mechanical excitation is also being assessed, to facilitate the formulation of a mathematical model to explain the dependence of measured macroscopic parameters on microscopic gel structure. Polyacrylamide gels have been used as model networks in these investigations, in part because of the technological importance of such polymers in biochemical separation procedures. Biological materials that have been studied by these techniques recently have included gels formed from glycoproteins obtained from sputum and clots formed from reconstituted human plasma (cf. project Z01 CT 00017-10 PSL).

Other activities mainly have involved obtaining information on particle size distributions needed by other investigators at NIH, including data on liposomes, 'coated vesicles' obtained from bovine brain and polymethane coating material scraped from implanted pacemaker electrodes. Collaborative studies to support the further development of a laser Doppler blood flowmeter also have been performed.

Publications:

- Chen, S-H., Chu, B., and Nossal, R. (Eds.): *Scattering Techniques Applied to Supramolecules and Nonequilibrium Systems*. NATO ASI Series B: 73, New York, Plenum Press, 1981.
- Nossal, R.: Laser Light Scattering. *Methods of Experimental Physics* 20: 299-336, 1982.
- Nossal, R.: Quasielastic Light Scattering from Polymer Gels. In Chen, S-H., Chu, B., and Nossal, R. (Eds.): *Scattering Techniques Applied to Supramolecules and Nonequilibrium Systems*. New York, Plenum Press, 1981, pp. 301-320.
- Nossal, R.: Stochastic aspects of biological locomotion. *J. Stat. Phys.* (in press).
- Nossal, R., and Jolly, M.: Shear waves and 'internal viscosity' in cylindrical gels. *J. Appl. Phys.* (in press).

INTERAGENCY SERVICE INFORMATION REQUEST PROJECT NUMBER (DO NOT use this space)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00021-11 PSL
DATES COVERED October 1, 1981 to September 30, 1982 TITLE OF PROJECT (40 characters or less) Correlation Function Spectroscopy/Laser Light Scattering		
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: R. J. Nossal, Ph.D., Research Physicist, PSL, DCRT		
COOPERATING UNITS (if any): Renner, Ph. D., BEIB, DBS; J. Gladner, Ph.D., LSC, NIADDC; M. Lewis, Ph.D., BEIB, DBS; R. Edlhoeb, Ph.D., CE, NIADDC; C. Steiner, Depart- ment of Chemical Engineering, University of Pennsylvania.		
LAB/BRANCH Physical Sciences Laboratory		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MATERIALS	PROFESSIONAL	OTHER
0.6	0.7	0.1
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (d) ANIMALS <input type="checkbox"/> (e) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords) Methods have been developed that utilize dynamic light scattering techniques to probe the mechanical rigidity and internal viscosity of polymer gels. Recent emphasis has been on characterizing changes in mechanical properties that occur near the gel-sol transition, as crosslink density and polymer concentrations are varied. The influence of solvent viscosity on the dissipation of mechanical excitation is also being assessed, to facilitate the formulation of a mathematical model to explain the dependence of measured macroscopic parameters on microscopic gel structure. Polyacrylamide gels have been used as model networks in these investigations, in part because of the technological importance of such polymers in biochemical separation procedures. Biological materials that have been studied by these techniques recently have included gels formed from glycoproteins obtained from sputum and clots formed from reconstituted human plasma (cf. project Z01 CT 00017-10 PSL). Other activities mainly have involved obtaining information on particle size distributions needed by other investigators at NIH.		
PHS-6048 (Rev. 2-81)		

Cell Motility and Chemotaxis

This project has been undertaken to study various aspects of cell locomotion, including the mathematical basis of macroscopic assays for leukocyte chemotaxis. Procedures for measuring parameters of cell migration, e.g., computer-assisted tracking techniques, have been developed.

Recent emphasis has been on perfecting laser quasielastic light scattering techniques for nonperturbative measurements of the mechanical properties of soft protein gels that, when examined by conventional rheometers, are structurally unstable (cf. project Z01 CT 00021-11 PSL). The objective is to examine cytoplasmic extracts from motile cells, in order to understand how the polymerization of cytoskeletal networks and the generation of contractile force therein actually takes place. In order to gain practical experience in acquiring such data, various measurements have been performed on polymer networks formed from fibrin, which in many respects is a similar but more readily available material.

NATIONAL SCIENCE FOUNDATION (N.S.F.) PROJECT NUMBER (Do not use this space)		N.S.F. DEPARTMENT OF HEALTH AND HUMAN SERVICES PHYSICAL SCIENCES DIVISION OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00017-10 PSL
PERIOD COVERED October 1, 1981 to September 30, 1982				
TITLE OF PROJECT (50 characters or less) Cell Motility and Chemotaxis				
FAMILY, LABORATORY AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT				
PI: R. J. Nozal, Research Physicist, PSL, DCRT				
COOPERATING UNITS (if any) J. Glader, Ph.D., LNC, NIADDK				
LAB/BRANCH Physical Sciences Laboratory				
INSTITUTE AND LOCATION Division of Computer Research and Technology				
TOTAL MANPOWER		PROFESSIONAL OTHER		
0.3		0.0		
CHECK APPROPRIATE BOX(ES)				
<input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER				
<input checked="" type="checkbox"/> (a) MINDS <input checked="" type="checkbox"/> (a2) INTERVIEWING				
SUMMARY OF WORK (200 words or less - underline keywords)				
This project has been undertaken to study various aspects of cell locomotion, including the mathematical basis of macroscopic assays for leukocyte chemotaxis. Procedures for measuring parameters of cell migration, e.g., computer assisted tracking techniques, have been developed.				
Recent emphasis has been on perfecting laser quasielastic light scattering techniques for nonperturbative measurements of the mechanical properties of soft protein gels which, when examined by conventional rheometers, are structurally unstable (cf. project Z01 CT 00021-11 PSL). The objective is to examine cytoplasmic extracts from motile cells, in order to understand how the polymerization of cytoskeletal networks and the generation of contractile force therein actually takes place. In order to gain practical experience in acquiring such data, various measurements have been performed on polymer networks formed from fibrin, which in many respects is a similar but more readily available material.				

PSL-0001
(Rev. 2-81)

Two-dimensional Fourier Transform Nuclear Magnetic Resonance Spectroscopy

Two-dimensional Fourier transform Nuclear Magnetic Resonance (NMR) spectroscopy has been applied to determine the structure of conjugates of glutathione and to study enzyme-catalyzed rates of exchange. Unidirectional rates have been determined for the phosphoglucose isomerase catalyzed isomerization and anomerization of glucose-6-phosphate and fructose-6-phosphate, for the adenyl kinase exchange of adenosine diphosphate to adenosine triphosphate with creatine to form adenosine diphosphate and creatine phosphate. From these studies mechanisms of the reactions were proposed and it was demonstrated that two-dimensional NMR spectroscopy is capable of monitoring simultaneously all of the pathways in a complex exchanging system.

Publications:

Jacobson, L., and Ferretti, J. A.: The determination of a phosphorus-phosphorus nuclear Overhauser enhancement by two dimensional magnetization exchange spectroscopy. *J. Amer. Chem. Soc.* (in press).
Marks, T. J., Pohl, L. R., Gillette, J. R., Hong, M., Hight, R. J., Ferretti, J. A., and Henson, J. A.: Stereoselective formation of bromobenzene glutathione conjugates. *Chem. Bio. Interactions* (in press).

NATIONAL SCIENCE FOUNDATION (N.S.F.) PROJECT NUMBER (Do not use this space)		N.S.F. DEPARTMENT OF HEALTH AND HUMAN SERVICES PHYSICAL SCIENCES DIVISION OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00025-07 PSL
PERIOD COVERED October 1, 1981 to September 1, 1982				
TITLE OF PROJECT (50 characters or less) Two-Dimensional Fourier Transform Nuclear Magnetic Resonance Spectroscopy				
FAMILY, LABORATORY AND INSTITUTION AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT				
PI: James A. Ferretti, Ph.D., Research Chemist, PSL, DCRT Lev Jacobson, PSL				
Other: R. S. Balaban, Ph.D., KE, NHLBI R. J. Hight, Ph.D., Laboratory of Chemistry, NHLBI L. R. Pohl, Ph.D., Laboratory of Clinical Pharmacology, NHLBI				
COOPERATING UNITS (if any)				
LAB/BRANCH Physical Sciences Laboratory				
INSTITUTE AND LOCATION Division of Computer Research and Technology				
TOTAL MANPOWER		PROFESSIONAL OTHER		
1.1		1.0		
CHECK APPROPRIATE BOX(ES)				
<input checked="" type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER				
<input checked="" type="checkbox"/> (a) MINDS <input checked="" type="checkbox"/> (a2) INTERVIEWING				
SUMMARY OF WORK (200 words or less - underline keywords)				
Two-dimensional Fourier transform Nuclear Magnetic Resonance (NMR) spectroscopy has been applied to determine the structure of conjugates of glutathione and to study enzyme catalyzed rates of exchange. Unidirectional rates have been determined for the phosphoglucose isomerase catalyzed isomerization and anomerization of glucose-6-phosphate and fructose-6-phosphate, for the adenyl kinase exchange of adenosine diphosphate to adenosine triphosphate with creatine to form adenosine diphosphate and creatine phosphate. From these studies mechanisms of the reactions were proposed and it was demonstrated that two-dimensional NMR spectroscopy is capable of monitoring simultaneously all of the pathways in a complex exchanging system.				

PSL-0001
(Rev. 2-81)

INTERMOLECULAR ENHANCEMENT PROJECT NUMBER (DO NOT use this space)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF INTERMOLECULAR RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00088-01 PSL
PERIOD COVERED October 1, 1981 to September 1, 1982 TITLE OF PROJECT (40 characters or less)			
Precision in the Measurement of NMR Parameters NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: James A. Ferretti, Ph.D., Research Chemist, PSL, DCRT Others: G. H. Weiss, Ph.D., Chief, PSL, DCRT J. E. Kiefer, PSL, DCRT L. Jacobson, PSL, DCRT			
COOPERATING UNITS (if any)			
LABORATORY Physical Sciences Laboratory SECTION			
INSTITUTE AND LOCATION Division of Computer Research and Technology ESTABL. MAINTENANCE: 0.1 PROFESSIONAL: 0.1 OTHER: 0.0			
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEWS			
SUMMARY OF WORK (500 words or less - underline key words) A study of the precision in the estimate of peak positions in spectroscopy was carried out. This study was carried out by considering both instrumental noise and error due to a finite digitization rate. Different strategies for estimating peak position were compared. The comparison showed that it is always desirable to use some form of curve fitting the peak rather than using the position of the digital maximum as the peak position estimate. It was shown that it is very difficult to estimate changes in peak position that are less than ten percent of the line width. A method for the estimation of peak areas for nuclear Overhauser enhancement factors was developed. Although this study constituted a preliminary investigation, which did not directly consider all sources of error, it was found that the peak area can be determined with high precision in the presence of substantial phase error. This method (called the product method) involves multiplying the peak height with the width at one-half peak height to compute peak area.			
PHS-4040 (Rev. 2-82)			

Precision in the Measurement of NMR Parameters

A study of the precision in the estimate of peak positions in spectroscopy was carried out. This study was carried out by considering both instrumental noise and error due to a finite digitization rate. Different strategies for estimating peak position were compared. The comparison showed that it is always desirable to use some form of curve fitting the peak rather than using the position of the digital maximum as the peak position estimate. It was shown that it is very difficult to estimate changes in peak position that are less than ten percent of the line width.

A method for the estimation of peak areas for nuclear Overhauser enhancement factors was developed. Although this study constituted a preliminary investigation, which did not directly consider all sources of error, it was found that the peak area can be determined with high precision in the presence of substantial phase error. This method (called the product method) involves multiplying the peak height with the width at one-half peak height to compute peak area.

Publications:

Weiss, G. H., Ferretti, J. A., Kiefer, J. A.: A study of precision in the measurement of chemical shifts. *J. Mag. Res.* 46:69-83, 1982.

INTERMOLECULAR ENHANCEMENT PROJECT NUMBER (DO NOT use this space)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL INSTITUTE OF INTERMOLECULAR RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00026-07 PSL
PERIOD COVERED October 1, 1981 to September 30, 1982 TITLE OF PROJECT (40 characters or less)			
Theory and Measurement of Intermolecular Forces NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: V. A. Parsani, Research Physicist, Ph.D., PSL, DCRT B. K. Lee, Expert, Ph.D., PSL, DCRT Others: D. Rau, Ph.D., NIADOK M. Proenty, Ph.D., NIADOK A. N. Schechter, NIADOK R. P. Rand, Ph.D., Brock University, Canada N. Fuller, Ph.D., Brock University, Canada			
COOPERATING UNITS (if any)			
LABORATORY Physical Sciences Laboratory SECTION			
INSTITUTE AND LOCATION Division of Computer Research and Technology ESTABL. MAINTENANCE: 3.5 PROFESSIONAL: 3.0 OTHER: 0.5			
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER <input type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEWS			
SUMMARY OF WORK (500 words or less - underline key words) During this year we have achieved the first direct measurement of a force between molecules. The repulsion between parallel DNA double helices is an exponentially decaying hydration force similar to that observed previously between bilayer membranes. Its magnitude depends strongly on the identity of ionic species bound to the DNA molecule. Its decay and lack of dependence on ionic strength show that at 0 to 20 Angstroms separations intermolecular forces differ qualitatively from the predictions of polyelectrolyte theory. The results correspond closely to an intuitive macroscopic theory of water polarization and work of water removal from molecular surfaces. Creation of protein gels and crystals under osmotic stress has enabled us to create the equivalent of phase diagrams for assembling proteins with the consequent determination of thermodynamic parameters. Molecular graphics on the DCRT and NIADOK systems are being used to visualize the molecular contacts corresponding to measurements of molecular assembly.			
PHS-4040 (Rev. 2-82)			

Theory and Measurement of Intermolecular Forces

During this year we have achieved the first direct measurement of a force between molecules. The repulsion between parallel DNA double helices is an exponentially decaying hydration force similar to that observed previously between bilayer membranes. Its magnitude depends strongly on the identity of ionic species bound to the DNA molecule. Its decay and lack of dependence on ionic strength show that at 0 to 20 Angstroms separations intermolecular forces differ qualitatively from the predictions of polyelectrolyte theory. The results correspond closely to an intuitive macroscopic theory of water polarization and work of water removal from molecular surfaces.

Creation of protein gels and crystals under osmotic stress has enabled us to create the equivalent of phase diagrams for assembling proteins with the consequent determination of thermodynamic parameters.

65

analysis of their contents (e.g., proteins on membranes or cytoplasmic organelles and structural elements).

All kinds of eukaryotic cells possess the capacity to control their form, their size and to regenerate lost parts. A general loss of these capabilities is characteristic of neoplastic cells. It seems, therefore, that there must exist in cells a mechanism for form control, a structurally continuous system that fills the cytoplasm and derives functional properties from its organization around a single center or complexes of many centers. Those units of organization, in addition to giving the cell its form, account for the nonrandom disposition of better-known organelles such as endoplasmic reticulum, Golgi bodies, microtubules, and to a lesser extent, mitochondria. We are constructing an image analysis with color graphics that will enable us to study the organization of cells in three dimensions. We use electron micrographs produced by the high voltage electron microscope (a national resource sponsored by NIH) in Boulder, Colorado and other micrographs taken at NIH. This concept of the cytoplasm is best illustrated by the red chromatophore of the tropical fish, *Holocentrus*. We already have initiated a study of the three-dimensional recontraction of the microtubule nucleation centers in these cells. These centers are dispersed in patterns that repeat from cell to cell.

In addition, using a stereo image analysis system and the PIC image processing system, we have measured the fractional volume of the various elements of the cytoplasm together with their surface area and the size of their pores. These results indicate that the microtubular lattice and the cytoskeleton occupy only a small fraction of the cytoplasm volume. These findings mean that these structures cannot physically obstruct the diffusion of molecules through the cytoplasm to a large extent but rather slow it by other means (e.g., chemical attraction). This result shows that the previous intuitive impression that these structures occupy a significant portion of the cytoplasm volume is not valid.

Diffusion of Molecules on Cell Surfaces and Light Scattering from Fluids

In this study we evaluated the effect of cell nonplanarity (e.g., due to the existence of microvilli and blebs) on the rate of diffusion of proteins and lipids in cell membranes using fluorescence photobleaching recovery. For simulated microvillous membranes, we found that the existence of curvature does not affect the measured diffusion coefficient by spot photobleaching recovery, contrary to naive intuition. On the other hand, diffusion along surfaces curved along one direction only depends strongly on the nonplanarity. It was found that the amount of nonplanarity needed to explain results of measured diffusion anisotropy in fibroblasts is far beyond what exists in nature.

In the second part, we derived hydrodynamic equations and the light scattering spectrum from microelastic fluids. We studied two cases, fluid-like and solid-like viscoelastic fluids.

Publications:

- Aizenbud, B., and Gershon, N. D.: Diffusion of molecules on biological membranes of nonplanar form - a theoretical study. *Biophys. J.* (in press).
- Aizenbud B., and Gershon, N. D.: Diffusion of Molecules on Microvillous Biological Membranes. In Perelson, A. C., DeLisi, C., and Wiegel, F. W. (Eds.): *Cell Surface Phenomena*. New York, Marcel Dekker (in press).
- Aizenbud, B., and Gershon, N. D.: Hydrodynamic equations and VH light scattering from viscoelastic (solid like) systems. II. Molecular approach. *Physica A* (in press).
- Aizenbud, B. M., and Gershon, N. D.: Hydrodynamic equations and VH light scattering from viscoelastic (solid-like and fluid-like) systems. Phenomenological approach. *Physica A* 107:126-142, 1981.

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL CANCER INSTITUTE INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00068-03 PSL	
PERIOD COVERED October 1, 1981 to September 30, 1982					
TITLE OF PROJECT (50 characters or less) Diffusion of Molecules on Cell Surfaces and Light Scattering from Fluids					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: N. Gershon, Ph.D., Visiting Scientist, PSL, DCRT Other: Boris Aizenbud, Ph.D., Department of Chemistry, M.I.T., Cambridge, MA					
COOPERATING UNITS (1 to 4) 					
LAB/BRANCH Physical Sciences Laboratory SECTION 					
INSTITUTE AND LOCATION Division of Computer Research and Technology TITLE: ANALYST: PROJECT LEADER: OTHER: 0.2 0.1 0.1					
CHOOSE APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) BLENDED					
<input type="checkbox"/> (a) (b) (c) (d) (e) INTERVIEW SUMMARY OF WORK (200 words or less - underline key words) In this study we evaluated the effect of cell nonplanarity (e.g., due to the existence of microvilli and blebs) on the rate of diffusion of proteins and lipids in cell membranes using fluorescence photobleaching recovery. For simulated microvillous membranes, we found that the existence of curvature does not affect the measured diffusion coefficient by spot photobleaching recovery, contrary to naive intuition. On the other hand, diffusion along surfaces curved along one direction only depends strongly on the nonplanarity. It was found that the amount of nonplanarity needed to explain results of measured diffusion anisotropy in fibroblasts is far beyond what exists in nature. In the second part, we derived hydrodynamic equations and the light scattering spectrum from microelastic fluids. We studied two cases, fluid-like and solid-like viscoelastic fluids.					
PUB-6040 (Rev. 2-81)					

INTERDISCIPLINARY SCIENCE INFORMATION EXCHANGE PROJECT NUMBER (Do NOT use this space)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL CANCER INSTITUTE INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00040-04 PSL	
PERIOD COVERED October 1, 1981 to September 30, 1982					
TITLE OF PROJECT (50 characters or less) Control of Actin Assembly in Nonmuscle Cells					
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: Stephen L. Brenner, Research Chemist, PSL, DCRT Other: E. D. Korn, Chief, LCB, NBLBI					
COOPERATING UNITS (1 to 4) Laboratory of Cell Biology, NBLBI					
LAB/BRANCH Physical Sciences Laboratory SECTION 					
INSTITUTE AND LOCATION Division of Computer Research and Technology TITLE: ANALYST: PROJECT LEADER: OTHER: 1.0 1.0					
CHOOSE APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER					
<input type="checkbox"/> (a) (b) (c) (d) (e) INTERVIEW SUMMARY OF WORK (200 words or less - underline key words) The protein actin is a major cytoskeletal component of all eukaryotic cells, serving both structural and motility-related functions. The G-actin monomer binds one ATP, which is hydrolyzed upon polymerization to polymeric F-actin. Studies in this laboratory are aimed at elucidating the detailed mechanism of polymerization, the role of ATP hydrolysis, and the cellular control mechanisms for actin assembly and disassembly.					
PUB-6040 (Rev. 2-81)					

Control of Actin Assembly in Nonmuscle Cells

The protein actin is a major cytoskeletal component of all eukaryotic cells, serving both structural and motility-related functions. The G-actin monomer binds one ATP, which is hydrolyzed upon polymerization to polymeric F-actin. Studies in this laboratory are aimed at elucidating the detailed mechanism of polymerization, the role of ATP hydrolysis, and the cellular control mechanisms for actin assembly and disassembly.

The actin polymer has two ends that, by virtue of ATP hydrolysis, can have different monomer/polymer equilibrium constants. As a result, actin monomers may treadmill through the filaments with net monomer addition occurring at one end of the filament and net loss at the opposite end while the filament maintains constant length. Direct evidence for treadmilling has been obtained this year using actin covalently modified with a fluorescent probe (N-pyrenylodo-acetamide) that has a 20-30-fold fluorescence enhancement when G-actin polymerizes. Trace amounts of this probe, when added to a G-actin/F-actin solution at steady state, are incorporated from the G-pool into F-actin with kinetics implying a treadmill mechanism. ATP hydrolysis rates, measured concurrently, indicate a high degree of efficiency for the treadmill, with as few as 1-2 ATP molecules hydrolyzed for every new actin protomer incorporated. The efficiency is a strong function of ionic conditions with no treadmilling occurring in the absence of free divalent cations. ATP hydrolysis is obligatory; no monomer incorporation occurs when G ADP actin is used. Cytochalasin, a drug that we have shown to cap the end of actin filaments, strongly inhibits monomer incorporation at steady state.

We are currently isolating several proteins from motile nonmuscle cells to determine their effects on actin polymerization, steady state monomer-polymer exchange, and nucleotide hydrolysis with the goal of understanding the control of assembly and disassembly of the actin filament in these cells.

Publications:

Brenner, S. L., and Korn, E. D.: Stimulation of actin ATPase activity by cytochalasins provides evidence for a new species of monomeric actin. *J. Biol. Chem.* 256:8663-8670, 1981.

Computerized Typesetting of Scientific Papers

The object of this project is to prepare computer disk or magnetic tape versions of scientific papers intended for publication. This material can be sent directly--on the phone or tape--to publishers' copyediting/typesetting computer systems.

Our current efforts emphasized facilitation of magnetic tape production and file preparation for transmission. This year we overcame formidable coding problems to write tapes, destined for outside use, on the IBM System 370 directly from WYLBUR files. We also initiated a series of telephone transmissions of WYLBUR files. Over 30 scientific articles have been transmitted this year either using one of the tape writing programs or by telephone.

Such electronic conversion of texts has been shown to be cheaper, faster, and more accurate than the old way of retyping material by the publisher. Typesetting costs can be halved. Already one journal is offering a major discount in page charges to authors submitting 'compuscripts.' Others should follow. The ultimate savings to NIH are expected to be significant.

NCI/NCRR/NCI/NCRR INFORMATION FORM PROJECT NUMBER (DO NOT WRITE IN THESE SPACES)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NCI/NCRR/NCI/NCRR INFORMATION PROJECT	PROJECT NUMBER Z01 CT 00066-03 PSL
PERIOD COVERED October 1, 1981 to September 30, 1982			
TITLE OF PROJECT (10 characters or less) Computerized Typesetting of Scientific Papers			
NAME, ADDRESS, AND INSTITUTIONAL AFFILIATION, AND TITLE OF PRINCIPAL INVESTIGATOR AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT PI: V. A. Parsegian, Ph.D., PSL, DCRT N. Crawford, Computer Assistant, PSL, DCRT M. McNeil, Computer Systems Analyst, Consultant Others: M. Douglas, Computer Systems Analyst, LAS, DCRT M. Horton, Computer Systems Analyst, LAS, DCRT			
COOPERATING UNITS (if any) Rockefeller University Press, Science Press, Biophysical Journal, Waverly Press			
LABORATORY Physical Sciences Laboratory			
INSTITUTION AND LOCATION Division of Computer Research and Technology			
TOTAL MAN-YEARS 0.6		PROFESSIONAL 0.3	OTHER 0.3
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) DISEASE			
<input checked="" type="checkbox"/> (1) MINDS <input type="checkbox"/> (2) INTERVIEW			
SUMMARY OF WORK (200 words or less - underline keywords) The object of this project is to prepare computer disk or magnetic tape versions of scientific papers intended for publication. This material can be sent directly--on the phone or tape--to publishers' copyediting/typesetting computer systems. Our current efforts emphasized facilitation of magnetic tape production and file preparation for transmission. This year we overcame formidable coding problems to write tapes, destined for outside use, on the IBM 370 system directly from WYLBUR files. We also initiated a series of telephone transmissions of WYLBUR files. Over 30 scientific articles have been transmitted this year either using one of the tape writing programs or by telephone. Such electronic conversion of texts has been shown to be cheaper, faster and more accurate than the old way of retyping material by the publisher. Typesetting costs can be halved. Already one journal is offering a major discount in page charges to authors submitting "compuscripts." Others should follow. The ultimate savings to NIH are expected to be significant.			
PHS-2046 (Rev. 7-81)			

1000

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

LSM activities can be divided into three areas: computation, consultation, and research.

Computation

A major part of LSM activity is the offering of statistical and mathematical systems/packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does support a system/package for the NIH community, it provides maintenance, documentation, instruction, and assistance for users to interpret the results.

Statistical Systems/Packages Support. During this year, as in the past year, the Statistical Software Section of LSM maintained the following program packages and programs:

- BMD, BMDP: Biomedical Computer Programs, UCLA.
- SPSS, SCSS: Statistical Package for the Social Sciences, SPSS, Inc.
- SAS, SAS/GRAPH, SAS/ETS: Statistical Analysis System, SAS Institute, Inc.
- P-STAT: Statistical Package, P-STAT, Inc.
- IMSL: International Mathematical and Statistical Libraries, IMSL, Inc.
- MSTAT1: Collection of Mathematical and Statistical Programs, DCRT.

During the year every system/package went through at least one major update. The SSS staff answered over 5,500 calls for assistance, and taught a total of twelve courses on these systems/packages; two each on the SPSS and BMDP packages and eight courses on the SAS system.

The use of program packages continues to increase. The average accesses per month of all the statistical packages rose from around 33,000 during FY81 to over 45,000 in FY82. For the sixth year in a row, SAS experienced the largest increase of any of the packages. SAS averages over 37,000 accesses per month, up from 24,000 per month in FY81. The average number of accesses per month for SPSS

decreased from 6,000 to 4,600. The average combined accesses of the BMDP and BMD packages was 2,500, about the same as in FY81. As an example of a package used for specialized purposes, PSTAT averaged 30 accesses per month, down from 60 average accesses per month in FY81. The main programs and subroutines in MSTAT1 averaged 1,300 accesses per month, in contrast with 650 in FY81. Accesses to the IMSL package cannot be counted, but it is estimated that usage increased during FY82.

The *DCRT Mathematical and Statistical Program Manual* was updated in FY82.

MLAB Support and Incorporation of C-LAB into MLAB.

The Biomathematics and Computer Science Section maintains the DECsystem-10 interpretive program MLAB, a package designed and implemented by BCS staff. During FY82, several hundred biomedical researchers at NIH used this package for modeling and graphical display tasks. MLAB is part of the NIH-funded Prophet system, the SUMEX-AIM system at Stanford University, and the NIH-EPA Chemical Information System. It has been distributed to various universities and research centers at their request. During FY82, BCS staff assisted in implementing overlay facilities on the DECsystem-10, and redesigned MLAB in a segmented form to use overlay. This reduces the load on the DECsystem-10, and user costs in many cases, because software for seldom-used operations is not loaded into computer memory except when it is needed. This made it possible to incorporate C-LAB, a previously independent package for clustering and multivariate data analysis, into the MLAB package. Other additions to MLAB were: new OMNIGRAPH character fonts for graphical displays of mathematical formulas or scientific text, and a new, more informative system of error messages. One advanced and three introductory courses were taught for MLAB. Two articles on MLAB techniques appeared in *INTERFACE*. The tenth edition of the

MLAB Reference Manual is being printed, and will be distributed in FY82.

Support for the Unified Generator Package. This package, developed by a BCS staff member, generates IBM System 370 assembly language programs. The compatibility of the package with new WYLBUR was maintained. As before, assistance was provided for users on request.

Support for Other Software. BCS continues to maintain certain special-purpose software and to assist users upon request. The PROLOG package, obtained from the University of Edinburgh, is designed for analysis of non-numerical data by aggregation of procedural rules; it has been used in LSM linguistic research. A program developed by BCS for interactive construction of an index for a document file has been supported. Various LSM-created programs for analysis and reconstruction of biological shapes using the symmetric axis method have been supported. A procedure simplifying the generation of users' IBM System 370 data set listings was developed and made available.

Consultation

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are successful, and are brief precisely because there is a known answer to the question posed. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

LSM consultations in FY82 were of the following types:

- Mathematical, statistical, and computer science advice with limited computer use (5%)
- Mathematical or statistical advice with considerable computer use (55%)
- Computational advice alone (40%).

The large computer use in these figures results from the continued availability and use of general purpose statistical and mathematical packages like SAS and MLAB. The diverse nature of LSM consulting is indicated by the projects and activities listed below.

Clinical Research, Patient Care, Epidemiology

Cancer Survival Study. R. Wesley (NCI/DCT/BRB). Patient survival-time data was analyzed. LSM assisted in modeling and nonstandard curve-fitting for maximum likelihood estimates of survival distribution parameters.

Obstetrical Care Study. P. Vietze (NICHD/MRDD). Long-term effects of two-day rooming-in after delivery were studied. Five categories of behavior

were monitored by an observer of experimental and control mother-child pairs at five time points from birth to six months. LSM assisted with statistical advice on design and data analysis.

Diagnostic Study of Systemic Lupus

Erythematosus. T. Chused (NIAID/LMI). Eleven clinical variables were evaluated, for ability to diagnose and estimate severity, in 87 patients with SLE plus a control group. LSM assisted in linear regression and discriminant analysis, which determined that a variable obtained as a ratio of cell counts was a good discriminator between the normal group and the SLE patients. Three presence-absence variables were significant in predicting this cell count ratio.

Laboratory Investigation

Anti-Bovine Gamma Globulin Radioimmunoassay.

Michael Miller (NIADDK/A&R). Tolerance to a thymic-dependent antigen was tested in autoimmune mice. LSM assisted in designing procedures using MLAB to prepare standard curves from control experiments.

Median Lethal Dose Analysis. R. Evarts (NCI/DCCP). Maximum likelihood estimates of median lethal doses (LD 50's) of compounds administered to groups of mice were calculated. LSM assisted in application of probit analysis techniques.

Multiple-Site Binding. J. Dunn (NCI/DCCP). In a series of chemical reactions, many F molecules bind stepwise to a G molecule, with distinct affinities. LSM assisted in modeling and analysis, using MLAB.

Receptor Characterization. M. Bissonette (NIADDK/DD). A mathematical model for the characterization of VIP and secretin receptors in rat pancreatic acini in terms of receptor number and receptor affinity was studied. LSM assisted in simultaneously curve-fitting several nonlinear functional forms to respective data, using MLAB.

Metal Ion Protein Binding. C. Chatterji (NIAID/LC). Optical absorbance experiments measured metal ion binding to a protein constituent of snake venom. LSM continued to assist in curve-fitting models to absorbance data.

Analysis of Simultaneous Binding Reactions. L. Jacobson (NICHD/LCP). Simultaneous binding reactions are studied by obtaining NMR scanner absorbances at specific frequencies. LSM continued to assist in mathematical modeling of equilibrium constant estimates.

Zinc-Activated Enzyme Model. P. B. Chock (NHLBI/IR/LB). A twelve-compartment model for zinc activation was studied. LSM assisted in developing combinatorial aspects of the model.

DNA Sequence Matching. P. Senapathy (NIADK/LEP). Various natural DNA sequences are studied in terms of sequence lengths between identical k-tuples. LSM provided software for generating gap statistics, and assisted in use of MLAB to compare data with negative binomial distribution models.

Bile Secretion Modeling. E. Feytmans (U. of Namur, Belgium). Secretion of bile under stimulation by taurocholate was measured in a patient population. LSM assisted in modeling and curve-fitting problems arising from delayed laminar flow in a catheter.

Duck Motion Study. W. Schleidt (U. of Maryland). Various aspects of duck motion were observed. LSM assisted in computer generation of graphical displays of idealized motions, using MLAB.

Induced Stroke Experiments. P. Ting (NINCDS/LNNS). Stroke was induced in one side at several sites in groups of dogs, and blood flow, pressure and blood gases were monitored. At several post-stroke sacrifice times the breakdown of the blood-brain barrier and related nerve damage were evaluated. LSM assisted with statistical advice on problems of experimental design and data analysis.

Program Management and Administration

Review and Verification of NRC Personnel Data. A. R. Frost, Jr. (NRC); C. Gellman (Technassociates, Inc.). Files of the NRC Automated Personnel System were reviewed, verified, and corrected. The Unified Generator Package was used to create software for updating the files and generating reports. LSM assisted in use of the package, use of generated programs, and in the design of related software. The resulting system was used on a production basis for over three months, with as many as six clerks working full-time to prepare input transactions, and performed completely satisfactorily.

Investigator Career Profile Study. F. Harding (NHLBI/DBDR); C. Crafford (JWK International). Data on investigators associated with NIH grants are evaluated for the effects of past NIH-supported training programs and assessments of national needs and currently available researchers. LSM provided assistance in the use of the Unified Generator Package to create data base software, in the use of generated updating, reformatting, and reporting systems, and in the training of users. Work

in the period covered by this report involved the addition to the data base of information on grantees in FY78, and preparation of reports analyzing this data.

Biomedical Communications Applications

Gastric Ulcer Data Base. C. Sniderman, S. Humphreys (NLM). Methods for natural language querying of gastric ulcer data are being developed. LSM assisted in design of a parser for English sentences and of related information retrieval routines.

Computer Research and Technique Development

Symmetric Axis Analysis. R. Webber, A. Davis (NIDR/CIBI). CIBI staff have developed a number of applications of the symmetric axis method for describing and analyzing biomedical images. LSM assisted in modifications of symmetric axis software and preparation of a PDP-11 export package for CIBI use.

Automated Data Processing of Medical Language

Research was continued on the compositional lexical semantics of medical terms derived from Greek and Latin. Medical compound words can be regarded as 'conjunctions' of larger semantic classes, represented by their Greek-Latin components. The relation between compound words and their constituents may be characterized as hierarchial. Medical compound words often represent certain units of meaning that could be likewise expressed by phrases consisting of separated components of compound words in English or other foreign languages. Additional standardization through medical compound word processing will be beneficial to retrieval performance.

A list was prepared of 40 semantically productive Greek and Latin terminal morphemes (-ITIS, -ECTOMY, etc.), the frequency of which was high. Medical compound words concurring with the selected terminal morphemes were analyzed according to semantic constituents and the compositional semantic patterns were established. The algorithm for semantic interpretation and paraphrasing of Greek-Latin terms into English was developed for -ITIS forms and surgical procedure forms (-ECTOMY, -STOMY, -TOMY, -PLASTY). The paraphrasing rules mentioned above will be used as a model for the development of additional paraphrasing rules for other medical components

derived from Greek-Latin. The development of paraphrasing rules will increase substantially the interpretive power of the lexicon and make it possible to interpret synonymous phrases that are not contained in the dictionary but that occur in medical context. Morphological analysis for the identification of productive terminal morphemes as markers of parts of speech classes, and the set of morphosyntactic transformation rules by which canonical nominal forms are derived from adjectives and noun plurals, were tested on the MEDLAR corpus. It was necessary to add 37 transformation rules to the existing tree to cover the MEDLAR corpus.

Work was continued on the preparation of syntactic and semantic rules for the Viral Hepatitis Data Base information system.

Proposed Course:

1. Combination of research studies in medical language at present level (morphology, syntax, semantics).
2. Creation of lexicographic data base to be used for the merge of medical dictionaries and extraction of microglossaries.
3. Continuation of collaboration in the encoding of surgical pathology data with the Laboratory of Pathology, NCI, to refine the medical dictionary and study the language of diagnoses.

Publications: None.

Cluster Analysis

The main objective of this project is the application of computer cluster analysis and related methods to NIH researcher problems. This year, nearest neighbor algorithms based on the latest published research and extensions to it were developed and tested, and algorithms for analyzing spacial point patterns were developed for testing patterns of retinal cones for regularity.

An improved algorithm for the computation of the Delaunay triangulation of a set of points was derived, programmed, and published. The dual of the triangulation is the set of Voronoi regions for the points. They define neighboring points and the nearest neighbor regions around each point. Measurements on the regions, e.g., areas and angles, can be used to test for randomness of a set of points.

The spacial pattern of blue cones, obtained from macaque retinas, appear to have some kind of regularity. Models of regular point patterns with different amounts of error were fit to the data in order to study the underlying nature of the regularity and to determine the amount of disorder. Three statistics based on nearest neighbor distances and angles between the pairs of points were used in testing models. Disturbed lattice models, using a regular lattice of points with random error at each point, could not be fit to the data. However, a model that considered each point (cone) as a soft ball with a minimum distance required between any pair of balls, fit the data very well.

Proposed Course: Other areas of the retina and other point patterns will be studied with this model to estimate the degree of regularity of cones in different regions of the retina.

Publications:

Shapiro, M.: A note on Lee and Schacter's algorithm for Delaunay triangulation. *International Journal of Computer and Information Sciences* (in press).

Yaar, I., Shapiro, M., and Pottala, E.: Spectral analysis of the EEG in hepatic encephalopathy treated with levodopa. *Electroencephalography and Clinical Neurophysiology* 52: 617-625, 1981.

CONTINUING SERVICE INFORMATION (SOURCE: PROJECT NUMBER (ON WFF use this source))	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE	PROJECT NUMBER
	INTRAMURAL RESEARCH PROJECT	Z01 CT 00001-11 LSM
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (40 characters or less)		
Automated Data Processing of Medical Language		
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT		
PI:	M. G. Facak A. W. Pratt Director	Computer Systems Analyst LSM DCRT OD DCRT
Other:	G. Dunham S. Harper Computer Programmer Computer Programmer	LSM DCRT LSM DCRT
COOPERATING UNITS (11 only)		
None		
LABORATORY		
Laboratory of Statistical and Mathematical Methodology		
SECTION		
Medical Information Science Section		
FACILITIES AND LOCATION		
DCRT, R1H, Bethesda, Maryland 20205		
TOTAL PAGES	PROFESSIONAL	OTHER
1-5	1-5	
CHECK APPROPRIATE BOX(ES)		
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN ISSUES <input type="checkbox"/> (c) NEITHER		
<input checked="" type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEWS		
SUMMARY OF WORK (200 words or less - underline keywords)		
<p>Research was continued on the compositional lexical semantics of medical terms derived from Greek and Latin. Medical compound words can be regarded as "conjunctions" of larger semantic classes, represented by their Greek-Latin components. The relation between compound words and their constituents may be characterized as hierarchical. Medical compound words often represent certain units of meaning that could be likewise expressed by phrases consisting of separated components of compound words in English or other foreign languages. Additional standardization through medical compound word processing will be beneficial to retrieval performance.</p>		

BIOETHICS COLLEGE INFORMATION TECHNOLOGY PROJECT NUMBER (DO NOT USE THIS SPACE)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE OFFICE OF INTEGRAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00009-08 LSM
PERIOD COVERED October 1, 1981 through September 30, 1982				
TITLE OF PROJECT (40 characters or less) Cluster Analysis				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT				
PI: M. B. Shapiro Research Mathematician LSM DCRT Other: F. de Monasterio Head LVR NEI S. Schrein Expert LVR NEI				
COOPERATING UNIT (if any)				
Laboratory of Vision Research				
LABORATORY				
Laboratory of Statistical and Mathematical Methodology				
SECTION				
Statistical Methodology Section				
INSTITUTE AND LOCATION				
DCRT, NIH, Bethesda, Maryland 20205				
TOTAL MANHOURS				
1.0 PROFESSIONAL 1.0 OTHER				
CHECK APPROPRIATE BOX(ES)				
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER				
<input type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEWS				
SUMMARY OF WORK (200 words or less - underline keywords)				
Nearest neighbor algorithms based on the latest published research and extensions to it were developed and tested.				
Algorithms for analyzing spatial point patterns were developed for testing patterns of retinal cones for regularity.				

PHS-0080
(Rev. 2-81)

Research Topics in Computer Science

The object of this project is to develop theoretical bases for new computer methods that will expand and improve the use of computing in biomedical computation. The methods used are the application of known algorithms and the development of new pertinent theorems involving combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern.

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is useful because such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

Currently, a study of hashing storage and retrieval methods is underway. This has resulted in the analysis of the performance of the hashing methods that resolve collisions using direct-chaining with coalescing lists.

Concurrently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently-introduced k-d tree method. Various improvements and refinements in both the algorithms and their analysis are being studied.

Much effort has gone into studying the B-Tree data structure for large files and developing a deletion algorithm to efficiently remove items from B-Trees.

Routines to store, retrieve, and delete items in a hash table, which employ direct-chaining with and without coalescing lists, have been prepared. The analysis of these algorithms has been recently completed and the results are to be published.

Publications:

Knott, G. D.: Fixed-bucket binary storage trees. *J. of Algorithms* (in press).
 Knott, G. D.: Graphics Facilities in MLAB. In Sproull, R. (Ed.): *Computer Graphics*, in Chang, S. (Ed.): *Handbook of Computer and Electrical Engineering* (in press).

BIOETHICS COLLEGE INFORMATION TECHNOLOGY PROJECT NUMBER (DO NOT USE THIS SPACE)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE OFFICE OF INTEGRAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00009-08 LSM
PERIOD COVERED October 1, 1981 through September 30, 1982				
TITLE OF PROJECT (40 characters or less) Research Topics in Computer Science				
NAMES, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT				
P.I. G.O. Knott Computer Specialist LSM DCRT Other: None				
COOPERATING UNIT (if any)				
None				
LABORATORY				
Laboratory of Statistical and Mathematical Methodology				
SECTION				
Biostatistics and Computer Science Section				
INSTITUTE AND LOCATION				
DCRT, NIH, Bethesda, Maryland 20205				
TOTAL MANHOURS				
0.3 PROFESSIONAL 0.3 OTHER				
CHECK APPROPRIATE BOX(ES)				
<input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER				
<input type="checkbox"/> (d) MINDS <input type="checkbox"/> (e) INTERVIEWS				
SUMMARY OF WORK (200 words or less - underline keywords)				
Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is useful because such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.				
Currently, a study of hashing storage and retrieval methods is underway. This has resulted in the analysis of the performance of the hashing methods that resolve collisions using direct-chaining with coalescing lists.				

PHS-0080
(Rev. 2-81)

TITLE DISCRETE MATHEMATICS AND APPLICATIONS		PROJECT NUMBER 201 CT 00011-08 LSM	
PERIOD COVERED October 1981 through September 30, 1982			
TITLE (if more than 100 characters, see 400)			
DISCRETE MATHEMATICS AND APPLICATIONS TITLE, LABORATORY AND RESEARCH AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATOR AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
P.I.: G. Hutchinson Research Mathematician LSM DCRT Other: None			
COOPERATING UNIT (if any)			
None			
LABORATORY Laboratory of Statistical and Mathematical Methodology			
SECTION Biomathematics and Computer Science Section			
FACILITY AND LOCATION DCRT, WTH, Bethesda, Maryland 20205			
TOTAL MATERIALS 0.4		OTHER 0.4	
(a) HUMAN SUBJECTS		(b) HUMAN TISSUES	
(c) HUMAN DATA		(d) HUMAN	
SUMMARY OF WORK (200 words or less - underline keywords)			
Inclusion relations between <u>vector spaces</u> and related problems concerning <u>modules over rings</u> were studied. Preparation of scientific manuscripts by <u>computer graphics</u> methods using <u>printer-plotters</u> on <u>minicomputers</u> was investigated.			

FORM 400
(Rev. 2-73)

Discrete Mathematics and Applications

The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics, and graph theory), and to apply such methods to problems of biomedical research and computer science.

Studies of inclusion relations between theories of modules over a ring continued. A manuscript prepared in the previous fiscal year was revised and accepted for publication. New research was directed towards (1) interrelating different mathematical theories of modules, (2) determining whether the lattice equations satisfied for a theory of modules was sufficient to determine all of the theory, and (3) classifying the rings that lead to the same module theory.

In computer science, the minicomputer software for computer generation of scientific manuscripts (text and figures) was completed and tested. Tests of the TEX system (developed at Stanford) for computer generation of scientific text were performed.

Proposed Course: Study of module theory will continue in the areas indicated above. Computer software to generate scientific manuscripts will be augmented by creation of mainframe software for high-speed generation of page displays using the advanced capabilities of Tektronix 4114 graphical display terminals.

Publications:

Hutchinson, G.: A complete logic for n -permutable congruence lattices.
Algebra Universalis 13: 206-224, 1981.

Hutchinson, G.: Exact embedding functors between categories of modules.
J. of Pure and Applied Algebra 25: 107-111, 1982.

Multivariate Statistical Analysis

The objective of this project is the study of multivariate ratios or proportions.

Study continued on multivariate statistical methods (size-shape methods) for analyzing ratios having a multivariate lognormal distribution. Studies also were continued on ratios that follow an Inverted Dirichlet distribution. A paper on special invariant discriminant analyses for size and shape variables (with J. N. Darroch) was written. The principal investigator presented a review of this work at Cornell University, Ithaca, N. Y.

Publications:

DeBlas, A. L., Ratnaparkhi, M. V., and Mosimann, J. E.: Estimation of the number of monoclonal hybridomas in a cell fusion experiment. *J. of Immunological Methods* 45: 109-115, 1981.

DeBlas, A. L., Ratnaparkhi, M. V., and Mosimann, J. E.: Estimation of the number of monoclonal hybridomas in a cell fusion experiment. In Vunakis, H. V., and Lagone, J. J. (Eds.): *Immunochemical Techniques* (a volume of *Methods in Enzymology*). Academic Press, New York, N. Y. (in press).

Mosimann, J. E., and Malley, J. D.: The Independence of Size and Shape Before and After Scale Change. In Taillie, C., Patil, G. P., and Baldessari, B. (Eds.): *Statistical Distributions in Scientific Work, Vol. 4, Models, Structures and Characterizations*. Dordrecht, Holland, D. Reidel Publishing Co., 1981, pp. 137-145.

Ratnaparkhi, M. V.: On splitting model and related characterization of some statistical distributions. In Taillie, C., Patil, G. P., and Baldessari, B. (Eds.): *Statistical Distributions in Scientific Work, Vol. 4, Models, Structures and Characterizations*. Dordrecht, Holland, D. Reidel Publishing Co., 1981, pp. 357-363.

Ratnaparkhi, M. V.: Some bivariate distributions of (X,Y) where the conditional distribution of Y, given X is either beta or unit-gamma. In Taillie, C., Patil, G. P., and Baldessari, B. (Eds.): *Statistical Distributions in Scientific Work, Vol. 4, Models, Structures and Characterizations*. Dordrecht, Holland, D. Reidel Publishing Co., 1981, pp. 389-400.

Roux, J. J. J., and Ratnaparkhi, M. V.: On matrix-variate beta type I distribution and related characterization of Wishart distribution. In Taillie, C., Patil, G. P., and Baldessari, B. (Eds.): *Statistical Distributions in Scientific Work, Vol. 4, Models, Structures and Characterizations*. Dordrecht, Holland, D. Reidel Publishing Co., 1981, pp. 375-378.

MATHEMATICS SERVICE INFORMATION LEADERSHIP PROJECT NUMBER (DO NOT WRITE THESE NUMBERS)		ALSO, DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE DIVISION OF INTERNATIONAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00013-08 LSM
FUNDING SOURCE DECEMBER 1, 1981 through September 30, 1982			
TITLE OF PROJECT (80 characters or less)			
Multivariate Statistical Analysis			
NAME, ADDRESS AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
PI: J.E. Mosimann Chief, LSM LSM DCPT Other: J.N. Darroch Flinders University, Adelaide, Australia M.V. Ratnaparkhi Associate Professor Wright State University Dayton, Ohio			
COVERING PERIOD (4 wks)			
None			
LAB/BRANCH Laboratory of Statistical and Mathematical Methodology			
SECTION Office of the Chief			
INSTITUTION AND LOCATION DCPT, NIH, Bethesda, Maryland 20205			
TOTAL PERSONNEL 0,3		[circle] PROFESSIONAL 0,3 [circle] OTHER	
CHECK APPROPRIATE BOX(ES)			
<input type="checkbox"/> (a) HUMAN SUBJECTS		<input type="checkbox"/> (b) HUMAN TISSUES	
<input type="checkbox"/> (c) MINORS		<input type="checkbox"/> (d) INTERVIEWING	
SUMMARY OF WORK (200 words or less - underline headings)			
The objective of this project is the study of multivariate ratios or proportions.			

PHS4040
(Rev. 2-61)

(TECHNOLOGY, RESEARCH, OR PROJECT NUMBER) (DO NOT WRITE IN THESE SPACES)	(NAME OF DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE) DIVISION OF INTERNATIONAL RESEARCH PROJECTS	PROJECT NUMBER Z01 CT 00039-05 LSM
PERIOD COVERED September 1, 1981 through September 30, 1982		
TITLE OF PROJECT (DO NOT EXCEED 80 CHARACTERS OR 1000 CHARACTERS)		
Linear Methods in Statistics		
NAME, ADDRESS, AND TELEPHONE NUMBER OF PRINCIPAL INVESTIGATOR AND ALL OTHER PARTICIPATING PERSONNEL (DO NOT EXCEED 100 CHARACTERS OR 1000 CHARACTERS)		
PI: J. D. Malley Mathematical Statistician LSM DCRT Other: None		
COOPERATING UNITS (if any)		
None		
LABORATORY OF STATISTICAL AND MATHEMATICAL METHODOLOGY		
SECTION: Statistical Methodology Section		
INSTITUTE AND LOCATION: DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANPOWER: 0.6 (INDICATE) OTHER:		
CHECK APPROPRIATE BOXES: <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input type="checkbox"/> (c) NEITHER		
() (a) HUMAN SUBJECTS <input type="checkbox"/> (a) HUMAN TISSUES		
SUMMARY OF WORK (200 words or less - underline keywords)		
Linear methods in statistics are applied to biomedical data analysis.		

PHS-00402
(Rev. 2-68)

Linear Methods in Statistics

Linear methods in statistics, as applied to biomedical data analysis, continue to be studied. Additional results were obtained on statistical and algebraic independence of random variables. A study of linear methods in variance component estimation was undertaken and a paper submitted for review and publication. Further, a new procedure was developed to treat unbalanced multivariate analysis of variance, and was submitted for review and publication. The method allows well-specified, rigorous tests of ANOVA models in the context of unequal cell sample sizes in the design layout; this is the most commonly occurring kind of data in the multivariate setting. The method was applied to schistosoma mansoni resistance to re-infectivity and the results were submitted to the *Journal of Tropical Medicine and Hygiene* as well as to a biostatistics journal.

Publications:

- Grimes, A. M., Mueller, H. G., and Malley, J. D.: Examination of binaural amplification in children. *Ear and Hearing* 2: 208-210, 1981.
- Malley, J. D.: Simultaneous confidence intervals for ratios of normal means. *J. of the American Statistical Association* 77: 170-176, 1982.
- Malley, J. D.: Statistical and algebraic independence. *Annals of Statistics* (in press).

Non-numerical Programming Techniques and Applications

Several applications of non-numerical programming techniques were pursued during the year. These projects involved use of the PROLOG and REDUCE computer languages, and the Unified Generator Package, and were mostly in the general area of computational linguistics. The two projects accounting for the most effort were an investigation into automated analysis of instructional text, and research on automatic interpretation of medical terminology in terms of the constituent morphemes of individual words.

Investigations into the development of a PROLOG program that can analyze material from an English-language textbook were continued during this reporting period. A program capable of analyzing paragraphs describing how to form legal BASIC expressions was extended into one capable of analyzing a discussion of the LET statement of the BASIC language. This extension involves the simultaneous treatment of syntactic and semantic considerations about the subject matter being 'comprehended' by the program. As a result of analyzing the textual material, the PROLOG program assimilates enough knowledge not only to parse, but also to interpret a LET statement. A detailed report has been written about this research, emphasizing the interconnections between syntactic and semantic concepts.

A second project in the area of computational linguistics involved the creation of a PROLOG program to analyze medical terms denoting surgical procedures in terms of their constituent morphemes (e.g., 'cysticolithectomy' is 'excision (-ectomy) of calculus (-lith-) from cystic duct (cystico-).' Six classes of surgical procedures were considered, an existing lexicon of morphemes was substantially enlarged, and the program/lexicon combination was tested on over 1,500 terms, taken mostly from medical dictionaries. Over 75 percent of the terms, including nearly all of those commonly used, can be interpreted automatically. The remainder presumably would have to be listed in a lexicon of whole words ('full forms').

Other efforts during this reporting period included the formatting and editing of a data base of surgical pathology summary diagnoses, which were then indexed using the Unified Generator Package to obtain frequency data on the terms used in the diagnoses. These and similar frequencies will be used in a forthcoming LSM project on word frequency distributions. For another project, the symbolic algebraic manipulation language REDUCE was used to assist in factoring a sixth-degree polynomial of interest in the theory of iterated maps on the unit interval.

Publications: None.

INTERCOMPARISON (CONSIDERATION EXCHANGE) PROJECT NUMBER (DO NOT USE THIS SPACE)	U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE BUREAU OF INTEGRAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT 00047-04 LSM
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (40 characters or less)		
Non-numerical Programming Techniques and Applications		
NAME, LABORATORY AND INSTITUTION AFFECTING TWO TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL INVOLVED ON THE PROJECT		
P.I. Other:	L.M. Norton M.G. Pacak J.E. Mossmann	Research Mathematician Computer Systems Analyst Chief, LSM
		LSM DCPT LSM DCPT LSM DCPT
COORDINATING UNIT (if any)		
None		
LAB/BRANCH Laboratory of Statistical and Mathematical Methodology		
SECTION Biomathematics and Computer Science Section		
INSTITUTION AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL REVENUE 0.6	PROFESSIONAL 0.6	OTHER
CHECK APPROPRIATE BOXES		
() HUMAN SUBJECTS	() HUMAN RECORDS	() BOTH
() (a) MINDS	() (a) INTERVIEW	
SUMMARY OF WORK (200 words or less - underline keywords)		
Several applications of non-numerical programming techniques were pursued during the year. These projects involved use of the PROLOG and REDUCE computer languages, and the Unified Generator Package, and were mostly in the general area of computational linguistics. The two projects accounting for the most effort were an investigation into automated analysis of instructional text, and research on automatic interpretation of medical terminology in terms of the constituent morphemes of individual words.		
PI-6886 (Rev. 2-83)		

Topics in Geometry and Analysis

The project objective is to develop mathematical and computational techniques using geometry and mathematical analysis, and to apply such methods to problems of biomedical research and computer science.

An algorithm for high accuracy identification and description of protein spots in two-dimensional electrophoretic gels was developed and coded. Testing of the program has begun.

In order to study convex cones a parametrization of all (non-isomorphic) N-algebras was studied. To determine smoothness properties of this parametrization and for its intrinsic interest a related set of Lie groups endowed with a left-invariant Riemannian geometry was studied.

At this point, the eye is the most accurate and effective detection device for protein spots in two-dimensional electrophoretic gels. The edges of the spots can generally be well fit by parabolic segments. An algorithm has been developed to model parabolic fitting by the eye utilizing a 'parabolic spacial second derivative' and other analogues of cues used by the eye. This has been coded as a Pascal program on a VAX computer. (This work is in collaboration with LGCB, NIMH.)

By developing alternate characterizations of some of the axioms of an N-algebra and studying N-algebra isomorphisms in these terms, a parameter space for the algebras can be constructed as the intersection of hyperplanes and a sphere in an appropriate vector space. A unique (with respect to N-algebra isomorphism class) parametrization space is then obtained as the quotient of the subset of the vector space by a tensor product of two lower dimensional orthogonal groups. By evaluating canonical Riemannian geometry of a cone of generalized positive definite symmetric matrices with respect to a particular field of bases, one uses the standard diffeomorphism from the triangular group of a T-algebra onto its related cone to endow the Lie group with a left-invariant Riemannian metric that is isomorphic to the geometry of the cone. This enables it to be seen that the parametrization is in fact polynomial.

Publications:

O'Connor, M. A.: Invariant metrics on cones. *Proc. of the Conference on Invariant Metrics and Holomorphic Maps*, Rome, Italy, Istituto di Alta Matematica F. Severi di C.N.R. (in press).

METROPOLITAN LEADERSHIP RESEARCH CENTER PROJECT NUMBER (See end of this report)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH NOTICE OF INVESTIGATIONAL RESEARCH PROJECT		PROJECT NUMBER	
				201 CT 00079-02 LSN	
PERIOD COVERED October 1, 1981 through September 30, 1982					
TITLE OF PROJECT (50 characters or less)					
Topics in Geometry and Analysis					
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT					
P. I.		M. A. O'Connor		Staff Fellow	LSN
Other:		C. R. Merrill		Senior Research Scientist	DCRT
		D. Goldman		Clinical Associate	LGCB NIMH
COOPERATING UNIT (if any)					
Laboratory of General and Comparative Biochemistry					
LAB Laboratory of Statistical and Mathematical Methodology					
SECTION Stomatognathic and Computer Science Section					
INSTITUTE AND LOCATION DCRT, NIM, Bethesda, Maryland 20205					
TOTAL OF PERSONNEL		PROFESSORIAL		OTHER	
CHECK APPROPRIATE BOX(ES)					
<input type="checkbox"/> (1) HUMAN SUBJECTS		<input type="checkbox"/> (2) HUMAN TISSUES		<input type="checkbox"/> (3) NEITHER	
<input type="checkbox"/> (4) MINDS <input type="checkbox"/> (5) INTERVIEWS					
SUMMARY OF WORK (500 words or less - underline keywords)					
<p>An algorithm for high accuracy identification and description of protein spots in two-dimensional electrophoretic gels was developed and coded. Testing of the program has begun.</p> <p>In order to study convex cones a parametrization of all (non-isomorphic) N-algebras was studied. To determine smoothness properties of this parametrization and for its intrinsic interest a related set of Lie groups endowed with a left-invariant Riemannian geometry was studied.</p>					

PHS-6440
(Rev. 2-81)

Data Management Branch

J. Emmett Ward, Chief

Clinical Research, Patient Care, Epidemiology

Clinical Support Section. During this past fiscal year a number of projects were developed and successfully completed:

- the development of a set of programs to translate and format MIS Raw Purged Data
- the development of a system of programs for preprocessing MIS Purged Data
- the design and development of a set of programs to build and update the integrated data base
- the writing of programs to translate and preprocess clinical laboratory data for the integrated data base
- the development of a procedure to automatically transmit chemistry and hematology data from the CIU data base to the PDP-10 System
- the transfer of data sets from mountable disk packs to mass storage, and
- the modification of a number of programs to support maintenance and retrieval of clinical data for the integrated data base.

BRIGHT STAT-PACK. Brian Cole, Jeanne Grillo (DMB/SAS); David Rodbard, Peter Munson (NICHD/BES); Jay Shapiro (CC). A computer system has been developed on the DECsystem-10 that enables Clinical Center investigators to analyze their own clinical data. Available thus far are t-test, basic statistics, weighted linear regression, chi-square, frequency distributions, and high-quality basic graphics. The system provides a convenient method of obtaining clinical data from the NIH Clinical Information Utility, and interfaces with both MLAB and SAS.

Effects of Bromocriptine on Schizophrenic Patients. Diane Feskanich (DMB/SAS); Neal Cutler (NIMH/BP). Statistical analyses were performed to study the effects of Bromocriptine on physiological and psychological variables. Camera-ready graphs

were produced, from which slides were made to illustrate a presentation by Dr. Cutler.

Survival System. Diane Feskanich (DMB/SAS); Ardyce Asire (NCI). This life table analysis system was originally developed in the 1960's to support the End Results in Cancer studies of NCI. Maintenance and improvement of the system is now the primary goal. The system has been sent to tumor registries and hospitals both in the U.S. and elsewhere. During FY82 the system was expanded to handle more than two racial groups.

Prevalence of Major Neurological Diseases:

Nigeria. Diane Feskanich, Jeanne Grillo (DMB/SAS); Bruce Schoenberg (NINCDS/NS); Dr. Osuntokun (University of Ibadan). This WHO-sponsored study consists of four parts: (1) census and health screen, (2) evaluation of risk factors, (3) neurological exam results, and (4) followup. A pilot study was done for Part 1 to determine validity and usefulness of questions and goodness of the questionnaire. During FY82 a new pilot was begun, based on information from the FY81 pilot. New forms were developed, and edit and update programs were written.

Alcohol and Memory. Mary Lee Dante (DMB/SAS); Elizabeth Parker (ADA). Test results from four types of tests measuring the performance of male college students under the effects of alcohol were computerized and scored, and a data base suitable for analysis was created.

Cerebral Palsy/Neonates. Diane Feskanich (DMB/SAS); Tatiana Kudrjavcev (NINCDS/NS). Ms. Feskanich received tapes of birth certificates and neonatal and fetal death certificates from the University of Rochester. During FY82 focus was on looking at low birthweight for age as a predictor of cerebral palsy in the newborn. Frequency distributions and counts were produced for this study.

Nutrient Data Base. Diane Feskanich (DMB/SAS); Elaine Offutt (CC/NUTR). The USDA nutrient data

base was obtained and programs were written to calculate nutrient intakes from daily foods records for research studies. A comparison of the numerous nutrient data banks available for purchase is being conducted to determine the one best suited for use in an interactive setting by Clinical Center nutritionists.

Combined Cardiology/Heart Surgery Data

System. Larry Martin (DMB/ASPS); Roger Dailey (DMB/DBAS); C. McIntosh, D. Rosing (NHLBI). This combined system provides a chronological record of the medical activity of NHLBI Cardiology and Heart Surgery Branch patients. In FY82 effort was directed toward meeting the routine and ad hoc reporting requirements and statistical needs of the NHLBI physicians and researchers. The system was expanded to include a graded exercise form and a physical examination form. A program and command processor were written to produce assorted bibliographies of pertinent papers and publications.

NIADK Study of the Incidence and Prevalence of Kidney and Urinary Tract Diseases in the Armed Forces. Darius Georg (DMB/ASPS); N. Cummings (NIAID). This study is being conducted to evaluate the research needs in this area and to correlate the research needs with the occurrence of morbidity and mortality of the disease. This system is currently in the raw data evaluation stage.

Sleep Study System. Darius Georg, Peter Basa (DMB/ASPS); Christian Gillin (NIMH/BPE). This system is being developed to provide a computerized method for scoring sleep data. Analysis and design have been completed. Programs to edit, update, and report on the data have been written. Other information such as drug administration and behavioral and clinical ratings may be added to the system at a later date.

Psychobiology Patient Information System.

Dennis George, Steven Soroka (DMB/ASPS); Frank Putnam (NIMH/BP). The purpose of this project is to condense a large amount of data for a small number of patients into a format that is useful for research analysis. During the last year the data was converted into a fixed format and programs have been written to produce reports in both hard copy and graphic form. This data was extracted from the CC/MIS data base.

Analysis of SLE Nephritis Patient Data. George Shakarji (DMB/OC); John Klippel (NIADDK). Collection of patient therapy data and implementation of our computer storage and retrieval system was begun. Complete chemistry and therapy data has been stored on over 100 SLE (Systemic Lupus Erythematosus) nephritis patients. Investigators

have had ready access to the data base to get up-to-date information and analysis on trends in patient progress.

Forecasting Trends of SLE Nephritis Patients.

George Shakarji (DMB/OC); John Klippel (NIADDK). Trend and forecasting analysis systems are being implemented to detect and forecast relationships among three groups of SLE patients, namely: those who are on dialysis, those who have doubled their creatinine, and a control group. Results from DNA Binding, Serum Creatinine, C3, Serum Albumin, Qual protein, RBC/HPF, and Hemoglobin are being analyzed for correlational relationships among these data. It is hoped that analysis will indicate and predict certain long term outcomes based on the relationships of these data in the three groups.

Subject Specific Reference Regions for Blood Chemistry Data.

George Shakarji (DMB/OC); Eugene K. Harris (DCRT/LAS). This study is a part of the continuing studies on defining reference regions, both univariate and multivariate, as applied to subject specific variability in clinical chemistry results for blood. Programs were written and completed to examine both theoretical and empirical properties: first through computer simulation, then by application to serial clinical assays collected over a long period of time (seven to nine years).

Analysis of Means and Variances of Chemistry

Data in Normal Subjects. George Shakarji, David VanSant (DMB/OC); Eugene K. Harris (DCRT/LAS). A package was designed and generalized to analyze serial measurements of analytes for within and across subjects. This package computes tests of normality for within-subject data, computes serial correlations and moments for each individual's data, and then proceeds to perform analysis of variance and covariance over all the subjects.

Dyslipidemia Computerized Recordkeeping

System. George Roberts (DMB/SAS); Ernst Schaefer (NHLBI/DMB). This system keeps records on clinical laboratory data for normal and dyslipidemic subjects and provides for routine reporting, ad hoc queries, and preparation of selected subfiles for statistical analysis. During FY82 work was begun on nutritional studies of these patients' diets. The analysis of the effects of Neomycin on cholesterol levels was also begun.

Penicillin Study.

Vivian Pelham, Charles Twigg (DMB/ASPS); Dorothy Sogn (DIR/NIAID). This system is being developed to collect data and provide reports from the clinical trials of skin testing with major and minor penicillin derivatives in hospitalized adults. Analysis and design were

completed during the year and the system is being implemented.

Laboratory Investigation

Smithsonian Tick Collection Query/Retrieval

System. Diane Feskanich (DMB/SAS); Carleton Clifford, Jim Keirans (NIAID/RML). The Rocky Mountain Lab has catalogued their tick collection on tape at the Smithsonian Institution. DMB is supplying the ability to update and query this file from Montana using the DCRT central computer facilities. During FY82 Ms. Feskanich installed interactive programs for data entry on the DataPoint word processor in Montana, ensured that the software would interface with DCRT software, and trained RML personnel in use of the software. She has also been acting as intermediary in the data flow between RML and the Smithsonian.

Monkey Management System. Diane Feskanich (DMB/SAS); Robert Williams (NICHD/PRB). A data base of the bibliographic and experimental history, plus the current medical status and experimental protocol for each monkey, was built. Programs were developed for data entry, editing, updating, and reporting. The system is being used to select appropriate individuals for specific experiments, and to prepare daily work assignments for caretakers and technicians. Future enhancements will include special reporting facilities.

Graphics. George Roberts (DMB/SAS); David Rodbard (NICHD/BES); Doris Wallace (DRG/RAE). Mr. Roberts has provided assistance to NIH research scientists and administrators who are learning how to use the new graphics capabilities. During FY82 he also began the development of a front-end package that will be able to accept existing sequential data files, apply user requested transformations, and produce TELL-A-GRAF data files. The user will be able to generate his own TELL-A-GRAF data file by supplying the appropriate algebraic equations in Fortran notation.

Molecular Modeling. Sigurd Knisley (DMB/SAS). During FY82 Mr. Knisley has been working on modifications to the shaded surface molecular display developed by Richard Feldmann and Tom Porter (DCRT). Currently available are a transparency option, which allows the viewer to see internal features or contact interfaces between molecules, and a variable illumination angle, which improves three-dimensionality.

Seroepidemiology Data Processing System. Judy Mahaffey (DMB/ASPS); Paul Levine (NCI). The Clinical Studies Section, NCI Laboratory of Viral Carcinogenesis, is trying to find characteristics of

serum samples that can be used to predict cancer. To this end, a computer system has been designed to manage all data necessary for efficient inventory control, test results feedback, and statistical analysis. The system is now operational and reports from the system are being sent to collaborating scientists in the U.S., Ghana, Greenland, and Singapore. During the past year a new contractor took over the running of this system. DMB provided assistance in setting them up to correctly run the system.

Primate Colony Carcinogen Study. John Parks (DMB/ASPS); Susan M. Sieber-Fabro (NCI/DCT). The purpose of this project is to develop a system to maintain and search data generated from a colony of approximately 2,000 nonhuman primates. The system as originally requested became operational during the last year. Future enhancements will be added as requested by user.

Canine Breeding Colony Data Processing

System. Peter Basa (DMB/DBAS); Dennis George (DMB/ASPS); T. Wolfe (DRS/VRB/ACS). The goal of this project was to develop a system to assist the Veterinary Resources Branch, DRS, with its recordkeeping and work scheduling. The system is complete. DRS is now in the process of installing a word processor system (CADO) in Poolesville to handle all data entry, maintenance, etc. When this is complete, DMB will work on interfacing the two systems.

Strain Specificities Reference System Steve Soroka (DMB/ASPS); David Sachs (NCI). A computer system is being developed for the Division of Cancer Biology and Diagnosis, NCI Immunology Branch, to assist in transplantation biology research. The system will be used to help locate existing congenic mouse strain products and/or to design mouse strain products having specific antigens that are used in experiments relative to the development of sera. The project has been temporarily suspended until new coding schemes and structures are developed and implemented by the sponsor.

Finite Element Package. David VanSant (DMB/OC); Warren Pince (NIEHS). This is an easy-to-use finite element program for solving a large class of elliptic (steady state), parabolic (time dependent), and equivalent partial differential equation problems in general two-dimensional regions. This package has a preprocessor program that allows the user to supply the problem description in a greatly simplified form so that no knowledge of FORTRAN is required. Graphical output can also be produced. Scalar, vector, and stress fields can be displayed via the Calcomp plotter.

Program Management and Administration

Administrative Data Base (ADB). Marvin Katz, Ron Wicks (DMB). This ongoing administrative project utilizes data base technology in support of NIH-wide materiel and financial management. As the Materiel Management System (MMS) entered its fifth year of development and operation, much time was spent in enhancing existing software. During FY82 some 50 change control items successfully went into production. Several new developmental efforts were implemented:

1. Requirements analysis for development of a data base Financial Management System (FMS) has been completed. It is anticipated that development of the FMS using contractor personnel will commence in late FY82.

2. Deployment of the delegated interface to MMS in the B/I/D Administrative offices continues. By the end of FY82 this effort will be essentially completed.

3. The development of the stock inventory system is proceeding. This system will be phased into production during late FY82 and FY83.

4. A vendor credit capability has been added to the accounts payable system.

5. An ability to search the NIH vendor data base using alphabetic names directly at the ADB terminal has been added.

6. The procurement system has been extended to include entry of DFM miscellaneous obligations and training orders. The online production of SF-147's has been added for reprints and for personal service contracts.

7. The requirements for open market requisition processing are being reviewed.

Full-Time Equivalency. Dennis George, Mike Letke (DMB/ASPS); George Roberts (DMB/SAS); John Hartinger (NCI/FMB). A system was built for monitoring the ceiling levels and full-time equivalency manyears for NIH. Data input, update, and query facilities are available, and report programs usable by all B/I/D's and by Central Budget have been provided.

DRR Grants Subproject System. Vivian Pelham (DMB/ASPS); Jean Babb (DRR). The existing DRR Grants Subproject System that used CPS was evaluated. A proposal was made for the redesign of this system to make use of more current, supportable technology. The proposal was accepted, and the system was developed and turned over to the user during the past year.

NIH Nutrition Grants Monitoring System. Judy Mahaffey (DMB/ASPS); Thomas Vogl (OD). A system has been designed for the NIH Nutrition

Coordinating Committee to assist them in monitoring and reporting data on biomedical and behavioral nutrition research at NIH and at other agencies within DHHS. The system is operational and Dr. Vogl's office is currently using it to answer inquiries from NIH directors' offices, the White House, Congress, and the public as they relate to dollar amounts and percentages of grant money being spent in the area of nutrition. This is an ongoing project with the data base being created each fiscal year.

Review and Evaluation Branch Grants Information System (GENIUS). Penny Brogan (DMB/ASPS); Harry Canter (NCI). The computerized Research Analysis and Evaluation Branch Information System, a highly specialized system, was designed and implemented for the Division of Cancer Grants, NCI. The system provides information on grants, contracts, intramural projects, and unfunded grants. The grants and contracts systems are 'generalized' so they can provide information from any NIH Institute. In the future, a Training Grants system will be developed, and history file maintenance must be added to the intramural projects and unfunded grants systems. Additional programs must be written to pick up more contract information from the NCI-CMS system.

NIH International Activities and Personnel Monitoring System. Penny Brogan (DMB/ASPS); Libby Low (FIC). A system provides the Fogarty International Center with the ability to maintain and query a data base with information on foreign scientists who are in the U. S. to perform health research. Most of these scientists are working at NIH. The system provides query capability as well as regularly scheduled preprogrammed reports. The existing system is being revised to include more accurate dating and editing capabilities, new reports, etc. Fourteen programs of the revised system are complete and operating. About sixteen programs still need to be written.

Employee Health System and Accident Reporting System. Vivian Pelham, Steve Soroka (DMB/ASPS); Julio Rivera, John Leach (ORS/S). A system is being developed to combine the employee health and accident reporting systems. Analysis and design has been completed and the system is currently being implemented.

Committee on Academic Science and Engineering (CASE) Reports. Darius Georg (DMB/ASPS); J. Bailey (OD/OPPE). This project involves a broad spectrum of data processing support required for the collection and reporting of DHHS obligations to institutes of higher education, research and

development centers, and nonprofit institutions. This is an ongoing project.

MMS Query and Reports. Jane Blessley (DMB/ASPS). This project is intended to provide an economical method for the selection and reporting of data from the NIH Administrative Data Base. Ms. Blessley provides recurring and ad hoc reports from the data base for all segments of the NIH community. During the past year she trained and turned over the responsibility for this project to another unit of DMB.

System for Controlling and Monitoring Complaints of Discrimination at NIH. Darius Georg (DMB/ASPS); G. Yee, M. Williams (OD/DEO). This project establishes and maintains a file that provides statistical data, on a case-by-case basis, of formal and informal complaints of discrimination at NIH. In the past year Mr. Georg revised and simplified the retrieval process.

System for Classifying NIH Research and Development Awards. Darius Georg (DMB/ASPS); William Rhode (OPPE/RA). The objective of this project is to test the feasibility of and then develop a computer system based on CRISP index terms for categorizing by basic research, applied research, and development and to show percentage distribution of dollars associated with each category. If the system proves feasible, the data will be used to prepare annual reports to the Office of Management and Budget (OMB) and the National Science Foundation (NSF).

ARMS/TDCS Interface (TAPS). Dennis George (DMB/ASPS); B. Hughes (OPA/P); A. Amatucci (OA/M). This project is intended to create an NIH Personnel System that is a composite of the current NIH personnel system (ARMS) and the DHHS Personnel System (TDCS). The system was completed and turned over to the Office of the Director/Systems and Action Branch during the year.

Radiation Safety Control System. Charles Twigg (DMB/ASPS); R. Zoon (DRS/RSB). This system is designed to monitor the use and users of radioactive isotopes at NIH. When complete, this system will include five subsystems. They are: (1) Inventory and Bioassay, (2) Lab Survey and Airborne Release, (3) Waste Processed and Activity Balance, (4) Training, and (5) Film Badges. In the past year, online collection and update of Form NIH88 was tested and implemented. Development of the lab survey and airborne release subsystem was begun. All subsystems except the Waste Processed and Lab Survey have been completed.

Electrical Safety Program System. Larry Martin, Steve Soroka (DMB/ASPS); Howard Metz (DRS/

BEIB). The chief of Scientific Equipment Services of the Biomedical Engineering and Instrumentation Branch has requested a system to help monitor maintenance of equipment at the Clinical Center. A system is being designed to computerize the results of routine electrical safety checks and of preventive maintenance performed on hospital equipment. The system will be used by DRS to schedule equipment checks, to provide reviews on instruments checked by contractors and by the Clinical Center, and to provide statistical information on repair histories of different types of equipment. The system was completed and turned over to the user during the year.

Interferon Production Monitoring System. Dennis George (DMB/ASPS); Hilton Levy (NIAID/LVD). The purpose of this project is to develop a system to monitor the production and subsequent use of interferon on an experimental basis. Various production techniques and use protocols are to be monitored in both human and animal subjects. Initial analysis and design have been started.

Information System of Extramural Scientists. Darius Georg (DMB/ASPS); William Rhode (OD/OPPE). This project involves the creation of a data base drawn from various sources to perform analysis of patterns of involvement in NIH science review activities by extramural scientists. The data base has been created and reports are being run as requested.

Medical Records Auditing System. Judy Mahaffey (DMB/ASPS); Gloria Burich (CC/MRD). The purpose of this system is to assist the Medical Records Department in the monitoring and reporting of the status of medical records from the time they enter the department until they leave. When the system is developed it should replace four manual systems now being used. The work-in-process portion of the system was completed during the past year. Work is now focusing on the 'audit' segment of the system.

AIRS Personnel System. Steve Soroka (DMB/ASPS); L. Lee Manuel (DCRT/OD). This project will involve a complete revision of the system due to the availability of the new TAPS file. Analysis, design, and implementation are currently in progress.

Biomedical Communications Applications

Selective Dissemination of Information. Sigurd Knisley (DMB/SAS). SAS has continued its support of the current awareness search for both Chemical Biological Activities (CBAC) and the Biosciences

Information System (BIOSIS). Retrospective searches are referred to the NIH Library staff.

Editorial Data Base Management System. Brian Cole (DMB/SAS); Judith Prewitt (DCRT/OD). A system is being built using the interactive capabilities of the DECsystem-10 that will allow professional journal editors and conference chairmen to track information on paper submission and refereeing.

Bibliographic Data Base. Sigurd Knisley (DMB/SAS); Curtis Harris (NCI/DCCP). Bibliographic information and keywords drawn from Dr. Harris' reprints of scientific articles were entered into the computer files. A system of searching this information and printing it for direct inclusion into book and journal bibliographies was set up using the powerful new tools available in WYLBUR.

Chinese Personalities and Institutions in Biomedicine. Judy Mahaffey (DMB/ASPS); Joseph Quinn, Joseph Lee (FIC). Due to a rapid increase in international exchanges in the field of biomedicine between the U.S. and the People's Republic of China, the Fogarty International Center has requested DMB services to design a system for the computerization of data on biomedical scientists and institutions in the PRC. The system will be used by the FIC officials in briefing NIH and non-NIH scientists interested in biomedical research in China.

Computer Research and Technique Development

SFOR (Structured FORTRAN) Compiler. Bob Magnuson (DMB/OC). The SFOR compiler, which generates block-structured IBM FORTRAN source code, was further enhanced to assist programmers' writing structured programs. There are six different kinds of blocks available to the FORTRAN programmer--CASENTRY, FOR, IF, LOOP, REPEAT, and WHILE.

RMAG Products Support. Bob Magnuson (DMB/OC). Necessary support is provided for RMAG, SLR, Logic Subroutines, Arithmetic Subroutine, SLANG, Voice Input, and SFOR. This ongoing support includes software maintenance, customer assistance, and the teaching of formal DCRT courses on the use of these products. In particular, a special effort had to be mounted to change over to the new WYLBUR format data sets.

PDOC: Program Documentation System. Bob Magnuson (DMB/OC). PDOC is a tool used to document programs. It is a front end to the WYLBUR Document Formatter, allowing the users to employ all of the Document Formatter's powerful features, while adding several useful enhancements of its

own. The PDOC system generates good-looking boxed comments that really stand out in explaining a program. PDOC permits symbolic referencing--forward or backward--of the generated code line numbers or of the generated document section numbers. There is a command for underlining. Various kinds of heads are created within the generated document, and are placed automatically within optional tables of contents. PDOC has an INCLUDE command, which permits inclusion of different files as parts of the PDOC source. A PDOC file consists of a source program to be documented to which you have added interspersed PDOC commands and WYLBUR Document Formatter commands. Hence, both the program and its documentation can be maintained within the same PDOC file. When running PDOC, the user can elect to have all or part of the contained code extracted and placed into an active file. There it can be compared, compiled, tested, saved, or run.

CP Tools. Bob Magnuson (DMB/OC). CP Tools is an integrated set of WYLBUR command procedures. Stored as members of a partitioned data set, only one of these tools need be accessed by a single user-defined command. When that tool is executed, it selects the tool actually wanted, passing along any included keyword parameters (taken from the command line argument). The tools include an NIH7000 editor that permits 'TV editing' of the user's data sets, combined with all of WYLBUR editing, plus 'token editing' (for changing variables or keywords without affecting other parts with identical substrings). Another tool gives online help on the various tools. Other tools include JCL generators for running SLANG and SFOR, as well as for microficheing any number of hold jobs. There are tools for setting the NIH7000 tabs as well as its PF keys to whatever the user wants. One of the tools formats text into TYPE commands with NIH7000 screen underlines, thus simplifying the task of creating screen help messages.

Computer Center Branch

Joseph D. Naughton, Chief

Summary of Projects

New Software.

TVEDIT, a powerful full-screen text editor, was made available on the DECsystem-10. TVEDIT provides an up-to-date, visible copy of the portion of the file being edited on the terminal screen. Nearly all of TVEDIT's commands are issued using labeled keys on the NIH7000 terminal keyboard, eliminating the need for memorizing commands. Editing changes are shown immediately, and the cursor may be moved to any location on the screen, making it possible for the user accurately to construct tables, diagrams, and flow charts. These features give TVEDIT remarkable versatility and ease of use.

POSTER was developed to fill the need for an easy way to prepare slides, posters, and transparencies of textual material for use as visual aids at scientific meetings and symposia. In the past, titles, captions, and summaries had to be hand-lettered or typed, photographed, and then enlarged. POSTER eliminates these steps and prepares posters directly or produces high quality copies for slides and transparencies. A variety of formatting capabilities, 24 typefaces, numerous specialized symbols, and commands for underlining and generating sub- and super-scripts are all available in POSTER.

The entire online data storage facility of the NIH Computer Utility was completely redesigned during the year. The installation of some 224 actuators IBM 3380 Disk Drives, together with the use of the 3850 Mass Storage System, provided a tremendous increase in capacity permitting the online storage of both larger and greater numbers of user data bases in a more reliable and cost effective manner. Three new data storage categories--Open, Controlled, and Dedicated--provide online data storage facilities for data sets ranging from a few bytes to more than 100 million bytes online DASD. The Mass Storage System provides online storage for data bases

exceeding this size. After extensive internal testing by the Computer Center, a plan to transfer all active user data sets to the new online storage structure was developed. Using a phased parallel approach with an elaborate back-up/recovery procedure some 300,000 online data sets were transferred during the last six months of the year with no interruption in service to users. The transfer will be completed during the early part of FY83. When complete, the NIH Computer Utility will have more than 141 billion bytes of online DASD data storage capacity available to users. It is anticipated that this, together with availability of some 236 billion bytes of data storage space on the Mass Storage System, will be adequate to meet users' needs for several years into the future.

Output Facilities. This past year saw the retirement of SPOUT, a facility that was originally designed to handle nonstandard output in an offline fashion. Improvements in the JES2 portion of the operating system and the use of high quality printing produced by the versatile 3800 laser printers made it feasible to allow the use of nonstandard forms online. Appropriate software changes were implemented gradually, and by July all standard forms as well as user-supplied forms became available online. Eliminating SPOUT reduced both processing overhead and manual handling of tapes, thereby increasing efficiency and accuracy. Two new CalComp 1055 Plotters replaced the old model 1036 plotters that had been in use since July 1977. The new plotters operate at almost three times the speed of the old ones and have the ability to plot in four colors. Better quality output and faster turnaround was provided to graphics users, at no increase in cost.

Communications Link. MERCURY, the communications link between the IBM System 370 and the DECsystem-10, is vital to obtaining the maximum effectiveness from both systems. Several hardware and software improvements were implemented this year to enable the MERCURY program to keep pace with new developments on the IBM System 370. The most significant enhancement allows the DECsystem-10 users to take advantage of the IBM 3850 Mass Storage System for infrequently-used data sets. As the year comes to a close, new hardware was acquired to improve both the speed and reliability of the MERCURY link.

Documentation and Publications. Providing current documentation for all services was an important challenge in this year of transition. *INTERFACE* continued to be the users' most important source of up-to-the-minute information. Eight issues and an Annual Index were published during the fiscal year. The Computer Center *Users Guide* also reflected the increased pace of change. For the first time it was completely revised twice within one year and required four updates to keep users informed of the most current and complete system technical details at all times. A new contract was established to make printing of the *Users Guide* more timely and reliable.

Other publications are oriented toward familiarizing users of the Computer Utility with the services, languages, and training available. Seven new publications were released this year and 12 others were either revised or updated.

User Training. A variety of intensive courses designed to acquaint the user with the computer services and languages available were offered through the Computer Center Training Program. The Training Program accommodated 2,244 students in 190 sessions of 64 different courses during the year. Special effort was made this year to designate courses at elementary, intermediate, and advanced levels, in order to meet the diverse needs of the user community.

Many extra sessions of the introductory WYLBUR courses were offered to make the capabilities of

New WYLBUR available to users. Other courses covered: the many computer languages used at NIH; the software packages available for statistics, computation, and graphics; and the operating systems of the IBM System 370 and the DECsystem-10.

Those unable to attend regular classroom courses were able to choose from 26 self-study courses, ranging from introductory surveys of computers and programming to advanced discussions of the IBM System 370 and DECsystem-10 operating systems.

Customer Assistance and Systems Maintenance. Customer assistance has always been an important part of the Computer Center's services, and even more so in FY82. The number of Programmer Trouble Reports (PTR's) researched and answered during the year rose to a record high of 5,148. This was partly due to the new, easier-to-use PTR command developed for WYLBUR. Although the Programmer Assistance and Liaison Unit continued to operate under restricted hours, it recorded more than 37,500 calls or visits from customers needing assistance.

Installation of new hardware and software on the IBM System 370 required significant changes to the operating system. The number of SYSGENS installed during the year rose to 106. Nearly 11,000 'fixes,' both preventive and corrective, were tested and applied to the system, and 10 new releases of current software packages were installed.

Research Projects

In addition to the many activities, services, and facilities it provides NIH, the Computer Center also serves biomedical computing with its research work in molecular graphics.

Computer Representation of Virus and other Macromolecular Assemblies

Over the past five years, a computer raster display has been used to represent the surface structure of macromolecules. Shaded spheres are the primitives of the representation. In globular protein and nucleic acid structures, each sphere represents one atom or at times one amino acid. In representing viruses, the sphere primitive has been used in some cases to represent one whole protein. In other cases, the spheres are used to represent the shape of a portion of a protein.

Symmetry of the viruses plays an important part in making the computer model look realistic. Once the shape of a protomer is modeled, it is then iterated over the (icosahedral) symmetry of the assembly. A model of limulus hemocyanin has been constructed starting from image-enhanced electron microscope data. Twenty spheres are used to represent the kidney bean shape of each of the 48 70,000-dalton proteins in the assembly. Fifty spheres were used to represent the low resolution shape of the muscle actin obtained from electron diffraction.

The generalization of surface shape representation obtained using spheres as primitives indicates that it will be possible to model subcellular organizations by computer.

Publications:

- Berzofsky, J.A., Buckenmeyer, G.K., Hicks, G., Gurd, F.R.N., Feldmann, R.J., and Mina, J.: Topographic antigenic determinants, recognized by monoclonal antibodies to sperm whale myoglobin. *J. Biol. Chem.* 257: 3189-3198, 1982.
- Feldmann, R.J., Potter, M., and Glaudemans, C.P.J.: A hypothetical space-filling model of the V-regions of the galactan-binding myeloma immunoglobulin J539. *Mol. Immun.* 18: 683-698, 1981.
- Pawlita, M., Mushinski, E., Feldmann, R.J., and Potter, M.: A monoclonal antibody that defines an idiotope with two subsites in galactan-binding myeloma proteins. *J. Exp. Med.* 1981: 1946-1956, 1981.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NATIONAL RESEARCH SERVICE		PROJECT NUMBER 201 CT09089-01 CCB
PERIOD COVERED October 1, 1981 through September 30, 1982		
TITLE OF PROJECT (40 characters or less) Computer Representation of Virus and other Macromolecular Assemblies		
NAME, GRADE, AND INSTITUTION AFFILIATION, AND TITLE OF PRINCIPAL INVESTIGATOR, AND ALL OTHER PROFESSIONAL PERSONNEL ENROLLLED ON THE PROJECT P.I. Richard J. Feldmann, CCB, DCRT, Computer Specialist		
COOPERATING UNIT (40 characters or less) None		
LABORATORY Computer Center Branch		
INSTITUTION AND LOCATION DCRT, NIH, Bethesda, MD 20205 TOTAL MONTHS: 1.0 PROFESSIONAL: 1.0 OTHER:		
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) HUMAN SUBJECTS <input type="checkbox"/> (b) HUMAN TISSUES <input checked="" type="checkbox"/> (c) NUTRITION		
<input type="checkbox"/> (d) MINORS <input type="checkbox"/> (e) INTERVIEW		
SUMMARY OF WORK (200 words or less - narrative suggested) Over the past five years, a computer raster display has been used to represent the surface structure of macromolecules. Shaded spheres are the primitives of the representation. In globular protein and nucleic acid structures, each sphere represents one atom or at times one amino acid. In representing viruses, the sphere primitive has been used in some cases to represent one whole protein. In other cases, the spheres are used to represent the shape of a portion of a protein. Symmetry of the viruses plays an important part in making the computer model look realistic. Once the shape of a protomer is modeled, it is then iterated over the (icosahedral) symmetry of the assembly. A model of limulus hemocyanin has been constructed starting from image-enhanced electron microscope data. Twenty spheres are used to represent the kidney bean shape of each of the 48 70,000-dalton proteins in the assembly. Fifty spheres were used to represent the low resolution shape of the muscle actin obtained from electron diffraction. The generalization of surface shape representation obtained using spheres as primitives indicates that it will be possible to model sub-cellular organizations by computer.		
PREPARED (Rev. 2-81)		

Office of the Director

Arnold W. Pratt, M.D., Director

Summary of Activities

Library Automation. E. Chu (OD); J. Mahaffey (DMB); J. Knight (CSL). In conjunction with other DCRT staff, the DCRT Librarian applies computer techniques to DCRT needs, advises other libraries, and maintains knowledge of work done outside NIH. In FY82 work on this project has been limited to a few modifications on the existing systems.

DCRT Publication File. K. Griffin, P.O. Miller (OD); R. Baxter (DMB). This ongoing project was begun in 1979 to create a file of citations for all papers published by DCRT authors. In FY82 additional work was done to correct errors in the file; a usable product should be available in the first quarter of the next fiscal year.

Electronic Typesetting Methods. P.O. Miller (OD). This project is an offshoot of work begun in 1979 as a part of a joint PSL/LAS/OD effort. It involves creating a specially-coded magnetic tape of WYLBUR text that can be used directly by computerized typesetting equipment at GPO. The technique has been shared with NIH and other Federal public affairs communities, through the NIH Printing Committee and the National Association of Government Communicators.

DCRT Communications Program. P.O. Miller, W.C. Mohler (OD). Previously called the DCRT Information Program, this is an ongoing project to develop improved and coordinated communication techniques to support DCRT activities. It has four parts: Analyzing Needs, Creating and Evaluating Products, Developing Resources, and Education. In FY82 work continued on developing and distributing products. As the OMB-imposed moratorium on publications and audiovisuals continues, new methods are being explored for communication between DCRT and the various groups that have needs for information about its work.

Clinical Data Management and Analysis. W.C. Mohler (OD); B. Cole (DMB); D. Rodbard (NICH);

J.R. Shapiro (Clinical Center). In spite of the rapid growth in use of data management and statistical packages provided for NIH scientists on DCRT computers, there is a perceived need for facilities that would be easier to learn and use in NIH clinical research projects. In FY82 work continued using BRIGHT, a table-oriented data management/analysis package on the DECsystem-10, developing added data analysis and display programs. Two presentations were made to medical staff fellows and other scientists with an interest in clinical data processing. Discussion began to examine the utility of a seminar series on clinical computer applications.

Multi-function Microprocessor Interface. A.W. Pratt (OD); D. Songco (CSL). This project, begun in FY80, seeks to adapt a variety of information acquisition techniques on a single microcomputer as a versatile data input/output interface for biomedical scientists and clinicians. Work in FY82 is discussed in detail in the Computer Systems Laboratory report.

Medical Linguistics. A.W. Pratt (OD), et al. This is a long-term project to define a set of semantic and syntactic forms that can aid in the analysis and interpretation of written medical statements.

Research Projects

Electronic Typesetting Methods.

Using the WYLBUR system, text is first collected and stored for publication production. Then, a magnetic tape of the data is furnished to GPO for direct typesetting input. Typesetting costs have been reduced eighty percent.

The technique has been made available to others in the public affairs community.

Future plans include exploration of interfaces to link equipment over telecommunications lines without hand-carrying tape, along with participating in the development of Gen Code, a proposed ANSI standard for encoding text for machine processing.

INSTITUTIONAL SERVICE INFORMATION EXCHANGE PROJECT NUMBER (DO NOT USE THIS SPACE)		U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE OFFICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00078-02 OD
PERIOD COVERED October 1, 1981 through September 30, 1982			
TITLE OF PROJECT (50 characters or less)			
Electronic Typesetting Methods			
NAME, LABORATORY AND INSTITUTE AFFILIATIONS, AND TITLES OF PRINCIPAL INVESTIGATORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT			
Patricia O. Miller Public Affairs Officer DCRT/OD			
COOPERATING UNIT (if any)			
Graphic Systems Development Division, U.S. Government Printing Office			
LAB/BRANCH Office of the Director			
SECTION Office of Scientific and Technical Communications			
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205			
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SUMMARY OF WORK (500 words or less - underline keywords) Using the WYLBUR system, text is first collected and stored for publication production. Then, a magnetic tape of the data is furnished to GPO for direct typesetting input. Typesetting costs have been reduced eighty percent.			
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Division of Computer Research and Technology
National Institutes of Health
Bethesda, Maryland 20205



Division of Computer Research and Technology

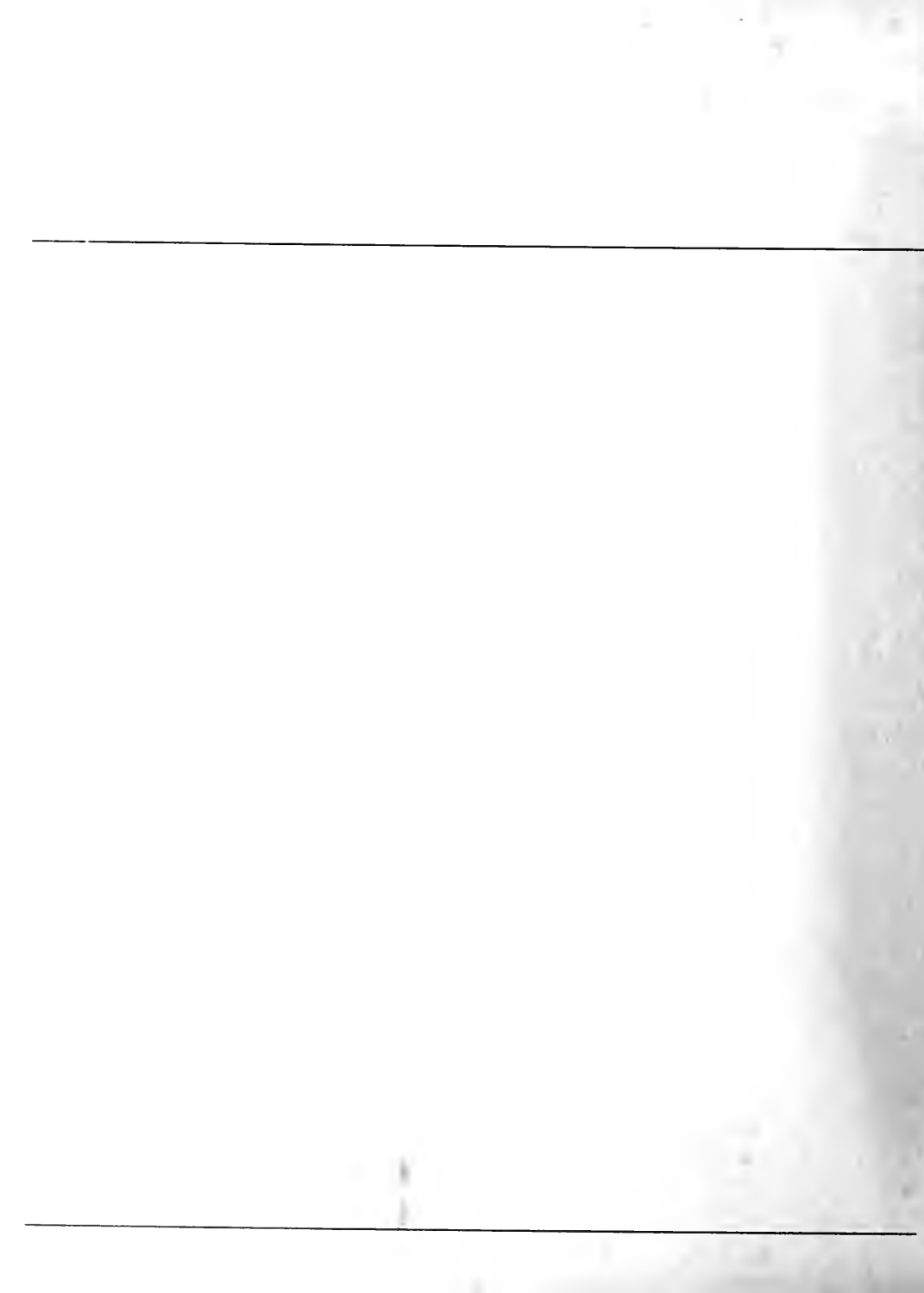
Fiscal Year 1983

Annual Report

Volume 1

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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Division of Computer Research and Technology

Fiscal Year 1983

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U.S. DEPARTMENT OF HEALTH
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Foreword

The Division of Computer Research and Technology has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH. DCRT serves as a scientific and technological resource for other parts of PHS, and for other Federal organizations with biomedical and statistical computing needs.

DCRT programs focus on three primary activities: conducting research, developing computer systems, and providing computer facilities.

The fiscal year 1983 annual report describes our work in two volumes:

Volume 1 gives an overview of the work of each group, highlighting the year's accomplishments;

Volume 2 gives details about the projects and activities of each group.

From the Director

During 1983 the Division of Computer Research and Technology was again broadly and actively involved in the conduct and management of science across all of NIH. The DCRT laboratories and branches are integral parts of the extensive biomedical computing activities within the core of NIH scientific excellence. Indeed, mathematics, statistics, engineering, and other elements of computer science are now recognized throughout the world as essential elements in biomedical science.

In 1963, when NIH first considered bringing these disciplines together in a new division, this was a novel idea. The concept has proved so successful that two decades later the task now facing us, DCRT and NIH, is to build upon the high level of technological success and move to one that can truly be called an Intellectual Era of biomedical computing.

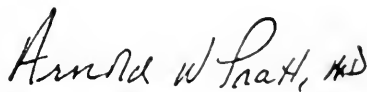
The Technological Era of computing is still a dominant force after three decades. Clever digital engineering continues to pack more processing power, storage, and communication capacity into smaller, cheaper, and eventually more reliable boxes. The plethora of new hardware is matched by new offerings of software.

However, better computer technology alone is not enough to create the intellectual linkage between the power of computing and the substance of modern science. The committee report in 1963 that led to formation of DCRT recognized this when it said at the outset:

The Committee was deeply impressed by the power of this technology and the promise it holds for contributing a new level of insight into problems in the life sciences. It was equally impressed by the magnitude of the resources...especially intellectual that its large scale application demands.

Results of great practical benefit in laboratories, clinics, and offices across NIH demonstrate the importance of mathematicians, engineers, and computer experts as intellectual resources in accomplishing that linkage. But the greatest benefits can occur only when an equivalent intellectual contribution emerges from the biomedical scientists in this collaboration. Then the intellectual union of computing and science can move forward to advance the underlying theory of biomedical science and to generate advances in the information sciences. Progress arises from the engagement of first class minds in a context where the focus on information processing is fully engaged in the environment of biomedical research.

The challenge to DCRT and NIH in 1983 is still the one presented in 1963, to amass and focus the best available intellectual resources on the important and pervasive opportunities for biomedical computing at NIH.



Arnold W. Pratt, M.D.
DCRT Director

Contents

Physical Sciences Laboratory	1
Laboratory of Applied Studies	5
Laboratory of Statistical and Mathematical Methodology	11
Computer Systems Laboratory	17
Data Management Branch	23
Computer Center Branch	27
Office of the Director	33

**MATHEMATICAL ANALYSIS BIOLOGICAL PHENOMENA
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CHEMICAL PROBABILITY DENSITY FUNCTION
MOLECULAR FORCE ELASTICITY CRYSTALLOGRAPHIC DATA
KINETICS HYDRATION**

Physical Sciences Laboratory

George H. Weiss, Chief

Function and Scope of Work

The Physical Sciences Laboratory works in areas of physics, chemistry, and applied mathematics relevant to problems in the biological sciences and medicine. Its program consists of two parts: internally-generated research, and consultation and collaboration with other NIH scientists in its areas of expertise.

PSL's program originally involved theoretical analysis only; it now includes a considerable experimental component as well. These experiments are in the areas of crystallography and light scattering and embody results originally developed theoretically by members of the laboratory.

The PSL staff consists of five professionals and several visitors who work in the areas of:

1. The structure and elucidation of forces determining the structure of membranes and other biological surfaces by a combination of crystallographic and thermodynamic methods.
2. Light scattering from biologically interesting systems, and the determination of dynamic properties of these systems by suitable interpretation of such experiments.
3. The use of image processing techniques for interpreting and reconstructing the three-dimensional structure of cells from multiple electron micrographs.
4. The application of the techniques of applied mathematics to problems in the physical and chemical sciences.

Because of the wide range of interests of members of the laboratory, a number of collaborative efforts, both with NIH scientists and with others, have been formed. Some of the data on intermolecular forces are being generated by scientists at Brock University, Canada. The electron micrograph images that are the experimental data for the image reconstruction project, are generated at the University of Colorado.

Techniques for the analysis and optimization of kinetic experiments are being developed in response to problems in nuclear magnetic resonance and positron emission tomography that have arisen at NIH.

FY83 Accomplishments

This year has seen the methodology used to measure forces between DNA double helices extended to the study of the effects of ionic species bound to the molecular surface. Further results using the technique developed by PSL members allow measurement of the pressure needed to pack DNA in a viral head. The experimental results suggest a variety of theoretical investigations on effects of hydration forces on bilayer deformation and on models of cell membrane fusion. A significant finding in this project is that the commonly accepted double-layer theory used to analyze forces in the immediate vicinity of membranes is badly in error and must be replaced by a more realistic theory.

Computational techniques have been developed for random walk models that have long been used in identifying crystallographic space groups from x-ray scattering data. Until now use of these models was restricted to a very small number of space groups, but the methods developed and still under development will allow routine use of statistical methods for the most commonly occurring space groups.

A study using light scattering techniques has been completed on the effects of subunit crosslinking on clot strength. These techniques are presently being applied to analyze the shear moduli of polymer gels, relating them to such system characteristics as crosslink density and polymer concentration. This investigation, when completed, will shed light on how such variables affect the dissipation of mechanical excitations.

A technique has been developed for the elimination of phase error in nuclear Overhauser effect measurements commonly used in nuclear magnetic resonance. Extensions of this technique will prove to be useful for the interpretation of kinetic data from two-dimensional Fourier transform NMR experiments.

A computer system has been assembled for three-dimensional reconstruction of cells from sets of electron micrographs.

**MATHEMATICAL ANALYSIS BIOLOGICAL PHENOMENA
MISTRY THEORETICAL ANALYSIS CELL LOCOMOTION
SESLASER LIGHT SCATTERING BIOCHEMISTRY CHEMISTRY
ROBABILITY DENSITY FUNCTION MOLECULAR FORCE
ELSCRYTALLOGRAPHIC DATA KINETICS HYDRATION**

HEALTHCARE
DATA
STATISTICS
MEDICAL
PRACTICES

WAREB
IVESB
DMATIC
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CHIVING

**SURGERY
EPTOOL
GLAMMIN
SOATAB
DCESSH**

PROGRAM
HQBCL
LITYFED
TOPERA
SERVICE

**INTERNATIONAL
MANAGEMENT
PHYSICS
POLYMER
RHEOLOGY**

Physical Sciences Laboratory

George H. Weiss, Chief

Function and Scope of Work

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Future Plans/Trends

Experimental work will continue on the use of combined thermodynamic and crystallographic methods for the measurement of intermolecular forces, particularly focused on the control and characterization of phase transitions in membranes and helical molecules. In conjunction with this, a systematic theoretical examination of several models of membrane fusion will be undertaken, taking into account the forces that have been identified in PSL measurements.

A molecular modeling study of the structure of sugars and polysaccharides will be begun. The structure of these molecules is not completely characterized because they are not crystallized readily. The study will make heavy use of the molecular graphics facility together with energy minimization and molecular simulations.

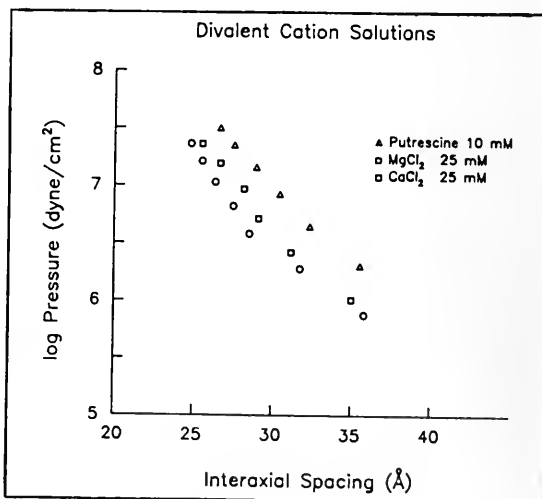
Work, both experimental and theoretical, will continue on the physical properties of biological polymer gels. Mathematical theories are to be developed relating to gelatin kinetics, to the coalescence of fibrils to form fiber bundles, and to the mechanical dissipation properties of idealized fibrin and actin lattices. In addition, theoretical studies will be initiated on the factors affecting the percolation of macromolecules through polymer networks.

In a collaborative project with NIADDK, LCP, PSL scientists have measured the forces between DNA molecules in aqueous solutions. This graph shows that the dominant contribution to the intermolecular force is the work of removal of water from the vicinity of the molecular surface. This observation is contrary to all previous expectations of polyelectrolyte interactions.

An investigation into practical computational techniques for detailing properties of random walks used in crystallography will be continued. Considerable success has been achieved in these calculations so far for a small number of space-group related random walks. Future study will be devoted to enlarging the catalog of results available to crystallographers.

A method for the three-dimensional reconstruction of cellular structure is being developed using electron micrographs. Software is being written for rotation of the resulting images. Further study will be devoted to estimation of the space available for diffusion in the cytoplasmic matrix.

Dr. Adrian Parsegian has been installed as President of the Biophysical Society. Dr. James A. Ferretti has taken a position as section chief in NHLBI.



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COMPUTER-BASED STUDIES MATHEMATICAL THEO
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Laboratory of Applied Studies

John E. Fletcher, Ph.D., Acting Chief

Functions

The Laboratory of Applied Studies (LAS) has three main purposes:

1. in collaboration with biomedical scientists, to apply mathematical theory and computing science to the development, testing, and improvement of mathematical models of physiological processes--particularly reaction-diffusion kinetics, transport and exchange of substrates in tissues, and the description of metabolism within cells and organs;
2. in collaboration with clinicians, to develop and apply mathematical or statistical theories and special-purpose computing procedures (analog or digital as required) to facilitate research projects aimed at improving diagnosis of disease, assessment of treatment, and understanding of basic physiological and pathophysiological processes;
3. to engage in applied research in mathematics, statistics, and computer science as necessary to provide a sound theoretical basis for collaborative studies, and to insure that state-of-the-art mathematical and computational methods are available as research tools at NIH.

Two sections carry out these primary LAS functions:

Applied Mathematics Section--AMS--(John E. Fletcher, Ph.D., Chief). This staff of five includes specialists in applied mathematics, computer science, biomathematics, and biomedical engineering.

Medical Applications Section--MAS--(James J. Bailey, M.D., Chief). This five-member staff includes physician-scientists, electronic engineers, and computer systems analysts.

Dr. Harris, former Chief, LAS is a biostatistician with training in public health and the basic medical sciences. He retired in early FY83 and continues in LAS as a part-time guest worker.

Scope of Work

The Laboratory of Applied Studies works on projects in basic and clinical biomedical science. Largely, these involve collaboration with other groups at NIH, elsewhere in the U.S.A., and abroad. The collaborating investigators this year included:

- clinicians in the Cardiology, Clinical Hematology, and Pulmonary Branches of NHLBI; in the Arthritis and Rheumatism Branch of NIADDK; and in the Critical Care Medicine and the Nuclear Medicine Departments of the Clinical Center
- physiologists and biomedical engineers at the Louisiana Technical University and elsewhere in the U.S.A. and Europe studying the transport of substrates within the microcirculation and the autoregulation of tissue perfusion
- biochemists and physicians at NIH, and at universities in the U.S.A. and in France working on models for receptors of drugs or other ligands, on the kinetics of enzymes in membranes, and on other problems in tissue metabolism
- electrocardiologists and biomedical engineers in the U.S.A., Canada, and Europe concerned with improved algorithms for computer-based interpretation of ECG's and evaluation of ECG interpretative programs
- clinical chemists and pathologists at NIH (Clinical Pathology Department, Clinical Center) and elsewhere in the U.S.A., in Europe, and in Japan engaged in the collection and study of reference values in laboratory medicine.

Highlights of the Year's Activities

Although FY83 was a transition year with retirement of some senior staff and departure of a visiting scientist, a number of collaborative projects made substantial progress.

In collaboration with NHLBI, a minicomputer-based laboratory system for studying delivery of oxygen to tissues during exercise through breath-by-breath analysis of pulmonary gas exchange has undergone extensive development in FY82-83. The equipment interfaces, designed and fabricated by Dr. E. Pottala in FY82, are now controlled by software interfaces linked to the main laboratory control programs.

Automatic operation of the entire system, including acquisition and analysis of ventilatory flow and gas concentrations, as well as control of the bicycle and treadmill, is now possible. Before this report is issued,

M. Horton expects to complete the systems programming that will allow automatic computation of noninvasive indices of patient functional status.

Serial measurements obtained in this exercise testing laboratory provide an objective indication of severity of disease and efficacy of treatment in patients with lung and blood disorders. Dr. R. Burgess, in collaboration with the Clinical Hematology Branch, NHLBI, is carrying out a study of drug therapy in patients with sickle cell disease.

In a joint project with the Nuclear Medicine Department, LAS has extensively analyzed the relationship of signal/noise ratios to harmonic content of regional time-activity curves in radionuclide ventriculography. Smaller regions were shown to have lower signal/noise ratios and a shift of harmonic content to higher frequencies, reflecting the effect of poorer counting statistics.

Theoretical work by Dr. M. Bieterman on the adaptive finite element (FEMOL1) methods for the solution of reaction-diffusion equations was essentially completed in FY83. These routines are now available on the NIH central computer systems. In addition, the IMSL routines known as TWODEPEP, finite element programs of a general type, have been implemented on the IBM System 370.

These programs are being work-tested on models of bioheat transfer in hyperthermia being studied by BEIB in collaboration with the Radiation Oncology Branch, CC, and on linear and nonlinear (Michaelis-Menten) metabolic models for tissue substrate diffusion and consumption.

B. Bunow and E. Pottala have studied network modeling languages and have demonstrated that network models are useful for biological simulation. Implementation of network modeling software on dedicated scientific computer systems such as the VAX 11/750-780 has made network modeling more available to investigators on the NIH campus and has established their utility on dedicated scientific computers. Some functional errors in the larger NET2 system were discovered in FY83.

The further use of this particular system on the IBM System 370 computer will depend upon correction of these errors by the package's developers. Presently, interested NIH scientists are being instructed in network methods, and exploratory applications are underway in collaboration with NIH researchers on problems of nerve conduction and of facilitated diffusion in tissues.

A considerable advantage of these modeling systems is that a functional rather than a mathematical description of the biological process suffices as a requirement to initiate study of its stimulus-response characteristics.

In FY82 a collaboration was initiated with FDA physiologists to use rodent ECG's as a means of testing for cardiotoxicity of drugs and fad diets (e.g., liquid protein). The frequency content of rodent ECG's has required redesign of instrumentation and development of wholly new ECG analysis software.

The rodent heart rate of 400-600 beats per minute produces ECG's with a much higher frequency content than that found in human ECG's. These signal analysis problems were largely resolved in FY83 and currently the ECG analysis of 38 animals before and during various levels of drug treatment is proceeding.

The LAS DeAnza image processing system has been upgraded from resolution of 256 x 256 pixels to 512 x 480 pixels. This upgrade will permit greater resolution and the development of more sophisticated algorithms for edge detection, image enhancement, and image manipulation.

During FY83 LAS staff members participated in various teaching and consulting, or advisory, activities.

J. Fletcher continued to serve as Chairman of the Mathematics and Computer Science Departments of the Foundation for Advanced Education in the Sciences. He is currently serving on a Planning Committee for the Director, DCRT; on a DRR ad hoc committee to design a workshop for the NAS Modeling Workshops; and as the DCRT representative to the NIH Advisory Committee for Computer Usage.

J. Bailey continued as a member of an NHLBI site-visiting team concerned with computer analysis of

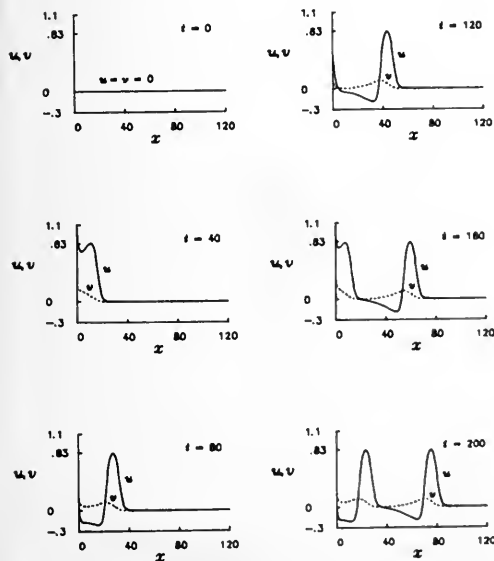
exercise ECG's. He also served as a consultant on Common Standards for Quantitative Electrocardiography, a program in medicine and public health, sponsored by the European Economic Community.

Since his retirement from LAS, former Chief E. Harris has continued to be a consultant in applied statistics to the Food and Drug Administration's Division of Medical Devices and Diagnostic Products. Dr. Harris also serves as consultant statistician to the College of American Pathologists, to the International Federation of Clinical Chemistry (Expert Panel on the Theory of Reference Values), and is a member of the Board of Editors of *Clinical Chemistry*.

Future Plans

The minicomputer system for analyzing pulmonary gas exchange in exercise will be tested on healthy volunteer subjects and on selected patient groups. Studies to evaluate cardiorespiratory abilities in patients and controls will be specified with protocols in cooperation with the Clinical Hematology and Pulmonary Branches of NHLBI.

The analysis of the signal/noise characteristics of various parameters of regional ventricular wall motion will continue jointly with the Nuclear Medicine Department, CC, and the Cardiology Branch, NHLBI, in an effort to refine noninvasive, differential diagnosis of coronary artery disease and cardiomyopathies.



Adaptive finite element methods are useful for solving reaction-diffusion equations. Here, the techniques solve a nerve impulse propagation problem.

A new project in cooperation with the Department of Critical Care Medicine, CC, to investigate dysfunction in neurologically impaired patients will move forward to integration and implementation of microcomputer-based methods for analysis and display of evoked potentials. This project was suspended in late FY83 because of procurement delays in hardware acquisition and by problems with the NHLBI equipment.

A major effort will continue the development of a language that will facilitate the conversion of network models simulating biological processes into forms compatible with languages such as MLAB, which will permit access to powerful data-fitting algorithms.

A scientific collaboration with the Yale University Computer Center is expected to result in new and improved numerical software for both the solution of linear equations and for systems of differential equations. The possibility of the incorporation of these routines into the MLAB modeling package will be explored.

The rodent ECG project is expected to extend to analyzing sequential changes in mice infected with pure strains of *Trypanosoma cruzi* (Chagas' disease). This extension of the rodent ECG project will be in collaboration with investigators from the World Health Organization and the Laboratory of Parasitic Disease, NIAID.

Utilizing the newly upgraded DeAnza image processing system, a joint study with the Clinical Neuropharmacology Laboratory, NIMH, will continue to develop theory and methods for interpreting electron energy loss spectra in intracellular organelles, particularly in the examination of dense bodies in electron micrographs of blood platelets.

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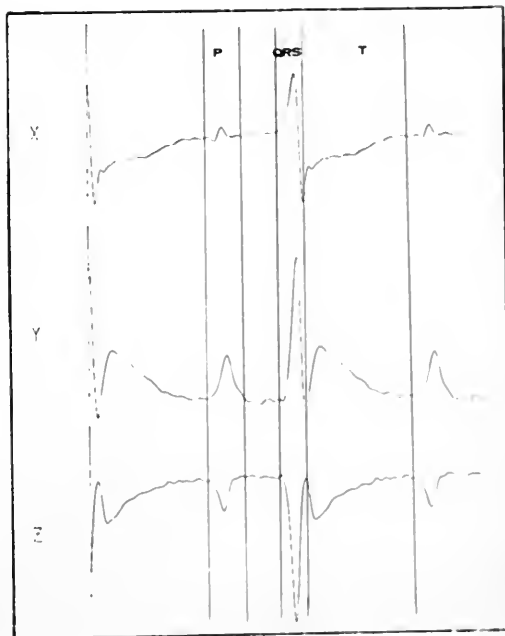
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LAS scientists and FDA physiologists are collaborating in a study of cardiotoxicity in rats, produced by drugs, food additives, or fad diets. This is a typical electrocardiogram taken from that study. The very high quality of this tracing is made possible by computer processing to extract a typical complex from the average of many cardiac cycles, thereby suppressing random muscle noise. This high quality is necessary in order to detect the earliest changes of cardiotoxicity.



MATHEMATICAL ANALYSIS BIOLOGICAL PHENOMENA
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EL SCRYTALLOGRAPHIC DATA KINETICS HYDRATION
COMPUTER BASED STUDIES MATHEMATICAL THEORY
PUTING SINGULAR VALUE DECOMPOSITION DATA
MATHEMATICS MEDICAL APPLICATIONS STATISTICS
N RECOGNITION IMAGE PROCESSING BIOMEDICAL
E SPARTIAL DIFFERENTIAL EQUATIONS ADAPTIVE

**PROGRAMS/PACKAGES STATISTICAL SOFTWARE
MLAB CURVE-FITTING NUMERICAL DERIVATIVES
TATISTICAL METHODOLOGY MEDICAL INFORMATICS
ATOR PACKAGE GRAPHICAL DISPLAYS LINGUISTIC
EDIC ALL LANGUAGE CLUSTER ANALYSIS DISCRETE**

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Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

Function and Scope of Work

The Laboratory of Statistical and Mathematical Methodology (LSM) combines research in mathematical statistics, mathematics, and computer and information science with collaboration and service in these areas to NIH researchers and administrators. LSM staff interact with all NIH Institutes, with other Federal agencies outside HHS, and with biomedical researchers worldwide.

In addition to the position of chief, the laboratory has sixteen full-time professional positions distributed among four sections:

The **Statistical Software Section (SSS)** provides consultation to and collaboration with NIH researchers and administrators in all computational aspects of biomedical data analysis, including selection and support of large systems/packages. Four specialists in scientific programming are led by a computer systems analyst whose specialty is statistics.

The **Statistical Methodology Section (SMS)** works closely with the Statistical Software Section. Three professionals in mathematical statistics provide biostatistical consultation and do independent research.

The **Biostatistics and Computer Science Section (BCS)**, directed by a mathematician, performs independent research and provides consultation and collaboration in the specialties of its five computer and mathematical scientists.

The **Medical Information Science Section (MIS)** investigates and develops methods for application of information and computer science to medical language data processing. Two computer specialists work under the direction of a computer systems analyst who is an expert in computational linguistics.

A major part of LSM activity is the offering of statistical and mathematical systems/packages to the NIH user community. LSM accepts responsibility for evaluation of new systems/packages and their suitability for NIH. When it offers a system/package to the NIH community, LSM makes three basic commitments:

1. Maintenance of the package, with adequate documentation, through NIH computer system changes, system/package updates, and corrections.
2. Rapid response to queries concerning user access to a system/package program, including job control language and program parameters.
3. Assistance in interpretation of results.

As a result of LSM's policy of not only supporting the use of these systems/packages but also aiding in the interpretation of their output, the statisticians of the Statistical Methodology Section provide consultation over a wide range of scientific fields. Some very brief consultations are very successful because there is a known answer to the question at hand. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

Research projects in LSM vary widely, from studies of natural language processing for medical information systems and studies of efficient algorithms for information retrieval to studies in mathematics and statistical methodologies for biomedical applications.

FY83 Accomplishments

FY83 was LSM's ninth year as a separate entity within DCRT. The volume of its computational and consultative services continued to expand; its research activities decreased slightly, with one project terminated.

Computation

During this year, the Statistical Software Section of LSM maintained the following systems/packages and programs on the IBM System 370 of the DCRT Computer Center:

- BMD and BMDP, Biomedical Computer Programs, UCLA.
- SPSS, SPSS-X, and SCSS, Statistical Package for the Social Sciences, SPSS, Inc.
- SAS, SAS/GRAPH, and SAS/ETS, Statistical Analysis System, SAS Institute, Inc.
- P-STAT Statistical Package, P-STAT, Inc.
- IMSL, International Mathematical and Statistical Libraries, IMSL, Inc.

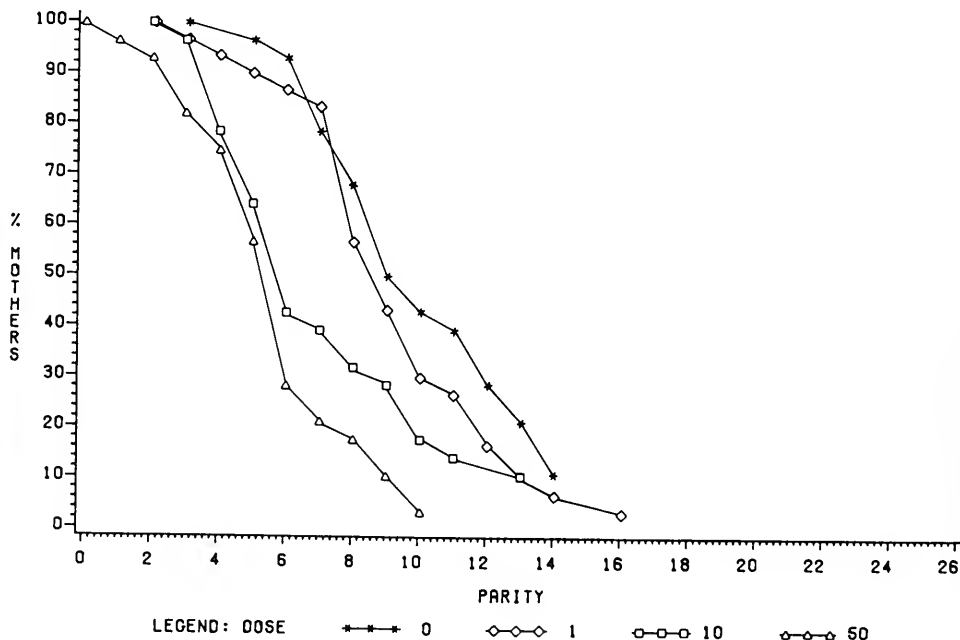
- MSTAT1, Collection of Mathematical and Statistical Programs, DCRT.

In FY83 the SSS staff responded to over 7,500 queries concerning use of these packages. Also during this year, BMDP and IMSL went through a major update. NIH served as a test site for both SAS82 and SPSS-X. Both systems will become production systems during the next fiscal year.

The Biomathematics and Computer Science Section maintains several systems/packages and specialized systems on the DECSYSTEM-10 of the Computer Center. Foremost in use is the interpretive system MLAB, designed (by LSM scientists) for biomathematical modeling, for cluster analysis by C-LAB operators, and for computer graphics. The Unified Generator Package, written and maintained by a BCS staff member, runs on DCRT's IBM System 370.

STATISTICAL ANALYSIS SYSTEM

STRAIN=B DRUG=B



SAS(Statistical Analysis System), which can be used to draw graphs like this one, is one of many software systems/packages supported by LSM.

LSM stresses the importance of teaching the effective use of systems/packages to the biomedical scientists and other users of DCRT.

In FY83, LSM continued to expand teaching and documentation for supported systems/packages. LSM taught eight introductory courses for SAS, two for SPSS, and two for BMDP. In addition, two introductory courses and one advanced course were taught for MLAB, plus four introductory courses on computer graphics at NIH. The second edition of the *Beginner's Guide to MLAB* is being printed now, and will be distributed before the end of FY83.

BCS staff augmented MLAB in FY83 by adding several mathematical operators and by adding facilities to permit numerical derivatives to be used for curve-fitting of large models. Also, color graphics and scientific text display were enhanced.

A separate program (GRAPH1) for easy generation of graphs was developed by SMS staff and is now being used by the NIH community. With only a small amount of user preparation, publication-quality graphs can be generated.

Consultation, Collaboration, and Research

LSM consultation and research in FY83 was closely tied to the use of the computer. Most consultations (55 percent) involved statistical advice combined with considerable computer use. Others (40 percent) involved computer use alone and a small fraction (5 percent) involved mathematical or statistical advice with only limited computer use. The percentages are unchanged from FY82.

In FY83, LSM research, collaborative, and consultative efforts were expressed in a number of studies. Statistical methodologies were developed for, or modified to suit, specific biomedical problems.

A study reported in FY82 was the subject of a publication, 'Statistical and Algebraic Independence,' in the *Annals of Statistics* in March 1983. This study contributes to a knowledge of properties of the sample covariance matrix, which is the basis for statistical discriminant analysis. Studies of discriminant methods continued in collaboration with Dr. J. Darroch, Flinders

University, South Australia, and Dr. H. Hoffman, DRS, including discriminant analyses of morphological variation in inbred strains of laboratory mice with reference to purity of breeding stocks. Collaborative work continued with Dr. P. Turkeltaub (BB/DPB) on clinical symptoms and allergic reaction to pollen. LSM participation in a study of Chagas disease (Dr. F. Neva, NIAID/LPD) was concluded when the edited tapes of data were prepared for the investigator.

Collaborative work in various studies of schistosomiasis (with Dr. A. Cheever, NIAID, LPD) continued. One portion of this research precipitated the development of a new statistical methodology that gives an exact treatment for a multivariate analysis of variance with unbalanced data. This analysis may be applied both to experiments with repeated measurements and to growth curve analyses. A paper on these results, which includes multivariate as well as nonparametric treatment of these designs, has been submitted to a statistical journal.

A study of nonparametric multiple comparisons was initiated in FY83, with particular attention being given to theoretical as well as to computer-simulated behavior of various procedures. The optimal selection of a sequence of items based on relative ranks with ties has been investigated, as well as an evaluation of tests for correlated proportions with incomplete data.

A collaborative study of the spatial distribution of blue cones in the retina with Dr. S. Schein (NEI/CB) and F. de Monasterio (NEI/LVR) was completed. It was possible to eliminate possible models on the basis of the several statistical techniques developed. Also, studies of 'size and shape' variables were continued. These studies provide methods for studying random proportions or ratios of common occurrence in biomedical data.

In computer science, work continued using PROLOG (the logical procedure language selected by the Japanese as the basis for their fifth-generation computer project), used here to formulate problems of medical linguistics. A program was developed to partially translate scientific text from an NIH input format to the input format used by the TeX manuscript

generation system at Stanford. Studies continued in data storage and retrieval and on mathematical questions concerning vector spaces.

In FY83 research in medical linguistics was continued on compositional morphosemantic analysis of medical terms derived from Greek and Latin. A methodology was developed for automated morphosemantic segmentation and semantic interpretation (paraphrasing rules) of medical compound words derived from Greek and Latin that denote surgical procedures. This methodology can be used with terms in the Systematic Nomenclature of Pathology (SNOP). The establishment of morphosemantic distribution patterns of medical compound words and the subsequent determination of semantic relations among them are crucially important for automated semantic interpretation of such words.

MIS also continued its collaboration with the Laboratory of Pathology, NCI and with the Clinical Support Section of the Data Management Branch, DCRT to maintain and improve the data base of Clinical Center surgical pathology reports. The automatic encoding system provided by MIS computed representations of the summary diagnoses of the surgical pathology report as written by the pathologist, in a language based on the SNOP vocabulary. Collaboration continued with Dr. Donald E. Henson, NCI, concerning changes in the SNOP dictionary.

LSM collaborative research on computer analysis of two-dimensional gel electrophoresis was discontinued due to the departure of the principal investigator. Results and computer programs were made available to NIH collaborative researchers.

LSM computer scientist Dr. Gary D. Knott received the Public Health Service Commendation Medal in June. The award was made for his continuing leadership and innovation in the development of MLAB, now used worldwide to advance science through biomathematical modeling and computer graphics.

Future Plans/Trends

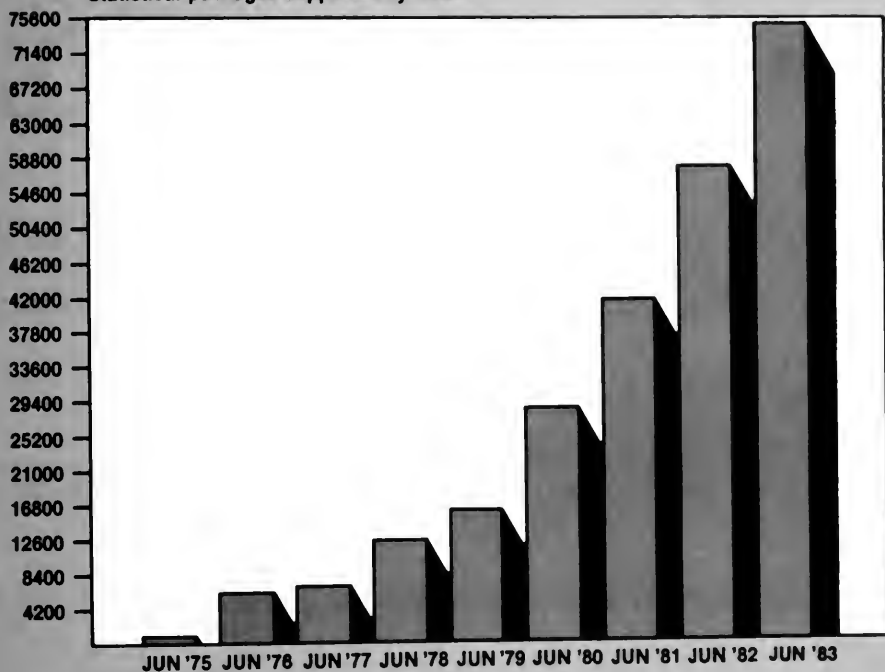
No major shift in laboratory service or research is anticipated in the coming year. Current levels of

statistical and mathematical systems/packages support, consultation, and user assistance will be maintained. Research projects will be continuations of those already initiated and reported here.

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Uses per month of
Statistical packages supported by LSM*



*Packages supported by the Statistical Software Section only. Does not include packages supported by the Biomathematics and Computer Sciences Section.

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Computer Systems Laboratory

Alan M. Demmerle, Chief

Function and Scope of Work

The Computer Systems Laboratory--28 professionals representing the disciplines of engineering, computer science, medicine, and chemistry--is the major source of expertise at NIH for minicomputer and microcomputer technology.

CSL engineers and scientists, in collaboration with NIH intramural laboratory and clinical investigators, apply this technology in the areas of laboratory automation and patient care. Some projects are occasionally undertaken with NIH extramural program staff and with other Federal agencies.

CSL's multidisciplinary approach aids both the recognition of problem areas that will benefit from automation and the interpretation of research needs in terms of computer methods.

Computers may be used only in an adjunctive manner--for example, as a more convenient means to acquire laboratory and clinical data--or they may be integral parts of an elaborate instrumentation system, such as a computer-controlled mass spectrometer. Advances in large-scale circuit integration (LSI)--the microprocessor revolution--have brought about the miniaturization of computer components and a dramatic decline in their prices and power requirements. CSL engineers are now able to use microprocessors to deal with problems that once defied solution because of cost, size, or manpower constraints.

CSL projects range in size from consulting activities of a few days' or weeks' duration to large-scale efforts taking many many years. Much CSL work involves the development of new methods or technology or is influenced strongly by the changing needs of research. Thus, it is often difficult to predict the long-term scope at the outset of a project.

FY83 Highlights

This year, CSL engineers and scientists worked on 28 projects, representing collaboration with almost all of the NIH Institutes. Some of these projects require only limited resources, while others take many many years. The latter deserve particular emphasis because of both

their sheer magnitude and the importance of the patient care or research activity they support.

One of these major projects involves the automation of flow cytometers/electronic cell sorters (FC/ECS). These instruments are being used increasingly in biomedical research, particularly in fields of laboratory research, and in clinical studies in immunology, cytology, and oncology. CSL support for these instruments began in 1973, when NCI requested development of a computer-based data acquisition, processing, and display system for the prototype flow cytometers developed at Stanford and Los Alamos Scientific Labs.

Over the years, a system has evolved that is based upon a Digital Equipment Corporation PDP 11/34 computer using an RT-11 operating system. System hardware includes a refresh CRT display, two disks, magnetic tape, 64K words of memory, incremental plotter, a link to the NIH Central Computer Facility, and an interface to the FC/ECS. Programs were developed to display the data as two- or three-dimensional figures.

Two-dimensional contour maps at user-selected thresholds are also available. Integration of selected curve segments and statistics describing peaks are included upon request. The various data presentations are a powerful tool to assist researchers in data interpretations. Equally important is the increase in the number of samples processed.

This system has been duplicated six times at NIH and the Naval Medical Center, and, in addition, many copies of the system documentation have been requested and sent to research centers in the U.S., Europe, and Australia.

In order to accommodate a high volume workload environment where sample throughput is important, a new FC/ECS Computer System was developed by CSL and installed at NCI during the summer of 1983. The new system uses a Digital Equipment Corporation PDP 11/24 (host) computer running under an RSX-11M multiuser operating system, Tektronix 4025 graphics terminals, and Digital Equipment Corporation LSI/11-23 (satellite) microcomputers for independent acquisition of data from each of several FC/ECS instruments.

The satellite computer sends acquired data through a high-speed direct memory access (DMA) link to the host computer where it is stored on magnetic tape or disk. The terminal at the satellite may be used for displaying acquired data. This is helpful in viewing collected data files immediately after they have been stored at the host. This terminal is also used during data acquisition for parameter entry, display of file recordkeeping, and error reporting.

Simultaneously with data acquisition, one or more users may analyze data at the host using independent graphics terminals. Processed files may be queued to a plotter so that a terminal can be used for further analysis while plotting proceeds. The new system can function with a PDP-11/34 computer, however, the PDP-11/24 supports more memory, and therefore more users may analyze their data concurrently. CSL anticipates the purchase of Digital Equipment Corporation's new 11/70 chip set, when it becomes available, so as to upgrade from the PDP-11/24 and further improve system speed and performance.

Another project requiring substantial investment of CSL manpower involves the development of a computer system for data acquisition, processing, and display, in support of the Electron Beam Imaging and Microspectroscopy Facility in DRS/BEIB. The Facility was developed by physicists, engineers, and computer scientists from BEIB and CSL as a research resource for NIH investigators. It contains an automated electron microscope system that can analyze and display a specimen's elemental chemical makeup as well as its morphological microstructure.

Electron energy loss (EEL) images, generated by measuring the characteristic amount of energy lost by beam electrons that interact with the atoms of a specimen, are thought to be the first in the world of this type produced on a scanning transmission electron microscope (STEM).

Another important development by project team members is a digital filtering technique to background-correct images produced by energy dispersive x-ray spectrometry (EDS). The presentation of this technique won the Corning Award for the best contributed scientific paper at the last Joint National Meeting of the

Electron Microscopy Society of America and the Microbeam Analysis Society.

During the past year, the first biological images were obtained showing calcium distributions in secretory ameloblasts. This study of the role of ameloblasts in tooth enamel formation, done in a collaboration between BEIB physicists and a NIDR visiting scientist, heralded the beginning of a shift from instrumentation and computer systems research and development to applying the system to biological research.

Subsequently, collaborations have begun with scientists from several other Institutes. NINCDS investigators are obtaining aluminum and calcium maps in cells taken from the hippocampus of victims of Parkinsonian dementia. Nitrogen and oxygen distributions in chromaffin cells are of interest to NIADDK investigators in a study of the release of epinephrine, and the Clinical Center is examining the relevance of magnesium in cardiovascular disease by studying the distribution of magnesium in individual lymphocytes.

To address some of the difficult problems presented by these and other studies, CSL presently is concentrating on improvements and refinements to the system data acquisition, imaging, and analysis capabilities.

Development of a new Image Processing Facility for NIH-wide use is another of CSL's major projects. Designed to complement an existing Evans and Sutherland System, which has in the past supported both image analysis and molecular graphics applications, the new facility has become operational this year. The main components are a Digital Equipment Corporation VAX 11/70 computer and a DeAnza IP8500 Image Array Processor. Although only one user station--comprising a 512 x 512 resolution color monitor with joystick and digitizing tablet--is currently available, two more stations are being procured and should be operational soon.

Software existing on the Evans and Sutherland System is being reprogrammed for the more powerful VAX machine, and new programs that utilize the extended capabilities of the DeAnza System are being developed.

The PIC software package, a mainstay of image processing users of the Evans and Sutherland System, is already operational, and is the backbone of scientific research on the new system. Current research centers in two fields. First, high resolution structural studies for several viruses (including vesicular stomatitis virus, bacteriophage T7, tobacco mosaic virus, and varicella zoster virus) are underway currently. Second, structural analyses of fibrous proteins such as keratin, vimentin, desmin, and actin are in progress.

These ongoing projects in macromolecular structural determination have placed NIH at the forefront of research in the analysis of high resolution electron micrographs.

As more and more images become available from an ever-increasing diversity of sources, the management of these images poses a considerable problem. This is particularly true in the NIH Clinical Center where it is desired that images obtained from a variety of modalities (CT, PET, NMR and Ultrasound Scans, Digital Vascular Imaging, etc.) be stored, transmitted, cataloged, and displayed at viewing stations in dedicated viewing areas and physicians' offices.

CSL has undertaken a study of the feasibility of implementing a picture archiving and communication system for the Clinical Center. Although the study has not involved a major CSL effort thus far, the implementation phases of such a network imply a massive investment of manpower over a protracted period of time.

The study has involved an investigation of the latest advances in data storage and local network technology. Optical laser disks, which will eventually enable up to one year's worth of images to be stored in one 'jukebox' system, are being considered, as are advanced local communications networks that permit the transfer of millions of bits per second. State-of-the-art image display and data management techniques will be needed and are being assessed. Funding and technological considerations may dictate phased implementation of such a system. Resource limitations may likewise require that substantial portions of the project be contracted out. The study is expected to provide the basis for such decision-making.

Future Plans/Trends

FY84 can be expected to present an increased demand for computers in laboratory and patient care settings. More complex research goals of biomedical research investigators point to a greater need for automation in the laboratory. Technological developments in large-scale circuit integration continue to lead to lower costs and smaller sizes for computers. The current popularity of 'personal' computers is resulting in greater awareness on the part of NIH scientists of the potential benefits of computers.

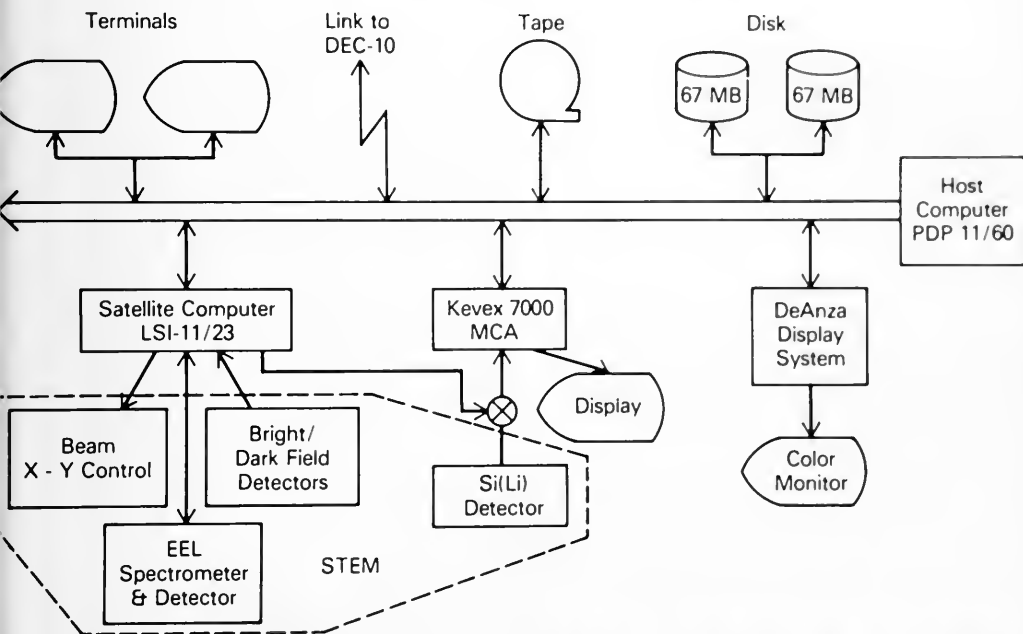
At the same time, CSL is faced with limited personnel and budgetary resources. In response to the challenge imposed by this conflicting set of circumstances, CSL expects to maintain high quality engineering and laboratory computer support to NIH programs by continuing policies developed in the past for managing resource issues. CSL staff will be deployed on projects promising maximum impact to the NIH community--those that serve a significant number of scientists, affect the quality of patient care, or represent general-purpose developments.

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STEM COMPUTER SYSTEM



A system for controlling an electron microscope's detectors and processing the data acquired from the detectors requires a considerable amount of computer hardware and software. The system developed at NIH for application in biology consists of a host computer and a satellite computer interfaced to a scanning transmission electron microscope (STEM). The STEM, which provides analytical signals, includes a magnetic sector electron energy loss spectrometer, an energy dispersive x-ray detector, and conventional bright and dark field detectors.

CLINICAL PHENOMENA
CELLULOLOCOMOTION
BIOCHEMISTRY CHEMISTRY
MOLECULAR FORM
KINETICS HYDRATION
THEMATICAL THEORY
POSITION DATA
STATISTICS
MEDICAL
ADAPTIVE
SOFTWARE
DERIVATIVES
INFORMATICS
LINGUISTIC
ANALYSIS DISCRETE
COMPUTER SYSTEMS
AUTOMATION
PROCESSOR SELECTION
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**CLINICAL SUPPORT CARDIOLOGY/HEART SURGERY
IT/NIH ADMINISTRATIVE DATABASE PDCCPT TOOL
GEMENTS SYSTEM APPLIED SYSTEMS PROGRAMMING
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BIBLIOGRAPHY SEA
PERSONAL COMPUTER SYSTEMS POLICY AND
COORDINATION FOR PLAN MANAGERIAL FUNCTION

Data Management Branch

J. Emmett Ward, Chief

Functions and Scope of Work

The Data Management Branch (DMB) provides advice and assistance to research investigators, program officials, and administrators throughout NIH in planning for and obtaining computer data processing services. In this role the branch is a central NIH resource for systems analysis, design, and programming. The Branch is also responsible for the development, maintenance, and processing of the NIH Administrative Data Base and the Clinical Center's Clinical Information Utility. There are currently 50 permanent full-time employees whose disciplines include computer science, mathematics, and statistics.

DMB staff design and create computer-based data management systems that provide practical solutions to the unique mix of administrative, scientific, and management data processing problems encountered at NIH. Each new computer system user is provided comprehensive training in all system facilities and functions of the system provided by DMB. In addition DMB staff teach courses about programming tools; provide advice on data management techniques to NIH programmers; serve as consultants to the B/I/D's for obtaining and monitoring contracting services for computer systems development; and create and maintain general purpose, user-oriented programming tools to speed building and improve operation of applications systems.

DMB comprises four sections. The **Applied Systems Programming Section (ASPS)** and the **Scientific Applications Section (SAS)** provide general computer systems analysis and programming services for all of the B/I/D's. The ASPS supports general data management, and the SAS handles those projects that require scientific data analysis.

The **Data Base Applications Section** develops and maintains the central administrative data base for NIH materiel and financial management. The **Clinical Support Section** develops and maintains the Clinical Information Utility as a data base for research and patient care in the Clinical Center.

FY83 Accomplishments

The Clinical Information Utility is a long term effort that, when completed, will provide a unique archive of integrated data for use in patient care and research. Efforts to date have involved:

1. the development of software to acquire and to make available data from the NIH Clinical Center Medical Information System and the individual clinical service activities
2. the integration of a number of these individual data bases, which allows random access to the integrated data, and
3. the development of software that enables users to make online requests for information and to receive automatically-generated retrievals of weekly, monthly, quarterly, and specified-time-period reports.

During FY83, the entire data base moved to Mass Storage; three access paths were developed to enable patient retrievals by way of the Registry File and the Inverted File and directly into the integrated data base; one conditional path was also added to allow access through the inverted file. Medications, vital signs, and Blood Bank data were added to the integrated data base, and automatic scheduling of weekly, monthly, and quarterly retrievals was implemented.

The NIH Administrative Data Base is an ongoing developmental project that uses data base technology in support of NIH-wide materiel and financial management. Significant progress has been made during the past year in several areas.

As of March 1983, DELPRO became fully operational throughout NIH. This effort places purchasing and receiving for delegated authorities in the B/I/D's, and it required the installation of 237 terminals and the training of more than 1,000 people. A new version of the central procurement system was implemented in May 1983. This new version is more efficient and has been designed to be highly portable and maintainable. Plans call for extending this software to accommodate the delegated functions.

Because of the need to conform to the Office of Management and Budget initiative on cash

management, a shift in priorities occurred on the Administrative Data Base. This shift has caused delays in implementing the Stock Requisitioning and Central and Self Service Stores Inventory systems.

Full cash management was achieved in the Accounts Payable System during FY83. These functions were phased in according to the requirements of the OMB mandate while improving support for Accounts Payable personnel.

Stock requisitioning software was completed in March 1983, and initial training and refinement of the training manual began in April. This system was made available to the B/I/D's in June for training. Central Stores and Self Service Stores inventory systems will be implemented along with stock requisitioning in October 1983.

Design of the new Financial Management System was received during March and April 1983. Several changes were required, and the system is now being programmed by the contractor. Interface requirements are being defined, conversion software is being designed, and structured test cases are being developed. Plans now call for implementation during the latter half of FY84.

Another project that should be of general interest at NIH has to do with the common problem of maintaining and easily retrieving bibliographic data. To resolve this problem DMB has been looking for an inexpensive method to store and retrieve personalized bibliographic data sets. Uses of the personal computer (PC), bibliographic services, and individual bibliographic references are being investigated. In a pilot test, DMB has been successful in downloading data from the Biosciences Information System (BIOSIS) to a PC, adding individual references and retrieving both, using the inverted techniques provided by a software product called SUPERFILE.

For years now, the Clinical Center Blood Bank has been manually preparing antibody identification panels to identify those red cells that would be most useful in finding compatible blood types for patients with 'unusual' antibodies. In a joint effort, DMB is attempting to computerize these accumulated years of knowledge

to both simplify and standardize the approach. To date, red cells to be included in antibody panels are being identified, and the Blood Bank and DMB are working together to investigate the nature of a panel so as to optimize its utility to identify and quantify those features that are most desirable.

For a detailed review of the many other important projects in which the Data Management Branch has been involved, please refer to the project reports in the *DCRT FY83 Annual Report, Volume 2*. These projects are too numerous to highlight in the summary.

In the area of general support for NIH activities, DMB continued to maintain and teach courses on the Inquiry and Reporting System (IRS) and MARKIV; to support NIH use of Chemical Biological Activities (CBAC) and Biosciences Information System (BIOSIS) current awareness searches on a biweekly and semimonthly basis, respectively; to maintain and distribute the NCI Survival System; and to consult with and assist NIH programmers and contractors, enabling facile use of DCRT computer facilities.

Future Plans/Trends

Plans with the ADB call for the development of the Market Requisitioning System during the next fiscal year with full implementation in early FY85. As usual DMB will implement this system in phases to make new capabilities available as early as possible. During the second half of FY84, DMB plans to start adding the inventories such as Clinical Center Pharmacy, Planning and Control Branch, Biomedical Engineering and Instrumentation Branch, and NIEHS to the ADB. Priorities for these inventories have not yet been established.

The Financial Management System will be added to the ADB during the latter half of FY84, and DMB will begin development of the new property system at that time.

Future CIU efforts will concentrate on improving data accessibility. For less complex retrievals by Medical Records personnel, a 'user friendly' retrieval assistance system will be developed. In a more general user sense, software will be developed to support ad hoc

formulation of retrievals, online definition of output formats and electronic delivery of output. As full integration of the data base nears completion, the classes of data that can be transmitted to the PDP-10 for subfile creation and analysis will be expanded.

Its role as a central resource for computer applications development throughout the B/I/D's will continue to receive primary support by DMB.

Publications

Data Management Branch July 1983

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The NIH Administrative Data Base July 1983

PANEL # 1 ANTIGEN PROFILE

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049364332	+	0	0	0	+	0	+	+	0	+	+	0	0	+	+	0					0	+	0	+						
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219204423	0	+		+	+	0	+	+	+	+	0	+	+	0	+	+	0	+	0	+	0	+	0	+				+		
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in cooperation with the Clinical Center Blood Bank, DMB is attempting to computerize reagent red cell selection used to find compatible blood types for patients with unusual antibodies.

**MAINFRAMESINTELLIGENTTERMINALSPROGRAMMI
IPROGRAMMINGTIMESHARINGTEXTEDITINGABCL
OCUMENTATIONCENTRALCOMPUTERUTILITYFED
IDESYSTEMRESEARCHANDDEVELOPMENTOPERA
PMENTSERVICESFEE-FOR-SERVICEUSERSERVICE**

Computer Center Branch

Joseph D. Naughton, Chief

Function

The Computer Center Branch, the largest component of DCRT, designs, operates, and maintains the NIH Central Computer Utility and its associated telecommunications facilities. The Center staff also provide direct support to the users of the Utility by conducting a formal computer training program, writing and publishing technical documentation, and providing programming assistance and consultation on the use of the Utility in support of scientific and administrative programs throughout NIH.

The NIH Computer Utility consists of two large multicomputer facilities designed around large scale IBM and DEC mainframe processors. The facilities are linked together by a complex set of communications facilities and are connected by telecommunications lines to thousands of remote interactive terminals and computers located throughout NIH and many other Federal agencies. The systems hardware is complemented by an extensive array of software that either has been designed and implemented by Computer Center personnel or acquired from other sources and adapted to meet the unique needs of the NIH biomedical research and administrative user community.

The Computer Center employs a highly specialized staff of professional, technical, and administrative personnel to ensure smooth functioning of the NIH Computer Utility 24 hours a day, seven days a week. Systems software is developed and maintained by a staff of experienced computer systems programmers and analysts, who also provide technical consultation, design and teach training courses, and write technical documentation describing the use of the Utility. The Computer Utility's hardware and telecommunications networks are operated and maintained by computer systems technicians and operations personnel. Data entry services are also provided. Systems design and management professionals are responsible for long-term program goals and the design integrity of the Utility. Because the Computer Center receives no appropriated funds from Congress, the design, operation, and maintenance of the NIH Computer Utility

is financed exclusively on a fee-for-service, cost-recovery basis.

The Computer Center also conducts a number of research and development projects to increase the effectiveness of computers in support of modern biomedical research. Current ongoing research projects include development of facilities that will enable microcomputers to be used in conjunction with the Utility; enhancements of output devices to permit the production of display mathematics and molecular graphics; installation of a data base management facility; and development of new training methodologies.

Scope of Work

Chartered as a Federal Data Processing Center, the NIH Computer Center plans, designs, implements, and operates a large, general-purpose central computer utility that provides a variety of computational services in support of a dynamic and diverse user community of over 13,000 research scientists, administrators, secretaries, analysts, and programmers throughout the Federal Government.

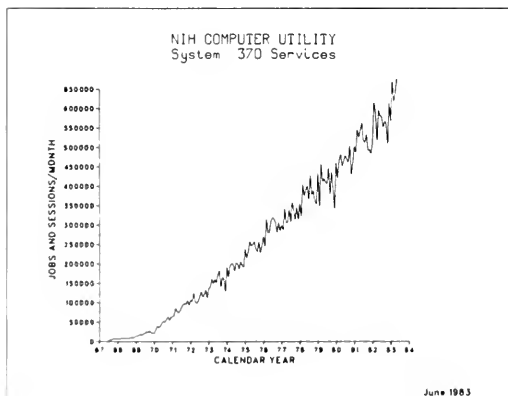
The primary component of the NIH Computer Utility is a uniquely configured multiprocessor computer system designed around five IBM 3081 processors with 144 million bytes of directly addressable main memory. The peripheral complex supporting the system includes 115 tape drives, 344 disk drives, 2 mass storage systems, 11 high speed printers, and card reader/punches, microfiche output units, and teleprocessing facilities serving over 1,000 communications lines.

Operating in a multiprogramming mode, this facility provides timesharing, text editing, and batch processing services, as well as microfiche, graphics, plotting, and data management facilities to users 24 hours per day. The IBM System 370 currently processes over 14,500 batch jobs and 13,500 interactive sessions daily. Over 7.3 million jobs-sessions were processed on the system during the past year, and more than 93.4 percent of these were completed and available to the user in less than two hours.

The other major component of the NIH Computer Utility, the DECsystem-10 timesharing facility, is designed around one DK and two KL-10 processors with five million bytes of directly addressable memory. This facility provides timesharing services and data communications support to over 2,000 laboratory research investigators throughout NIH. Ten tape drives, 31 disk drives, and a variety of teleprocessing equipment make up the peripheral complex. Over 120,000 interactive timesharing sessions were processed on the DECsystem-10 during the past year.

Use of the NIH Computer Utility has grown steadily since its inception in 1967. An average of 28,944 job-sessions were processed each day on the Computer Utility during FY83. This represents an 11.5 percent increase over last year.

The computing power of the NIH Computer Utility can be accessed from several thousand interactive terminals and 160 remote job entry computers located in users' offices and laboratories throughout the United States.



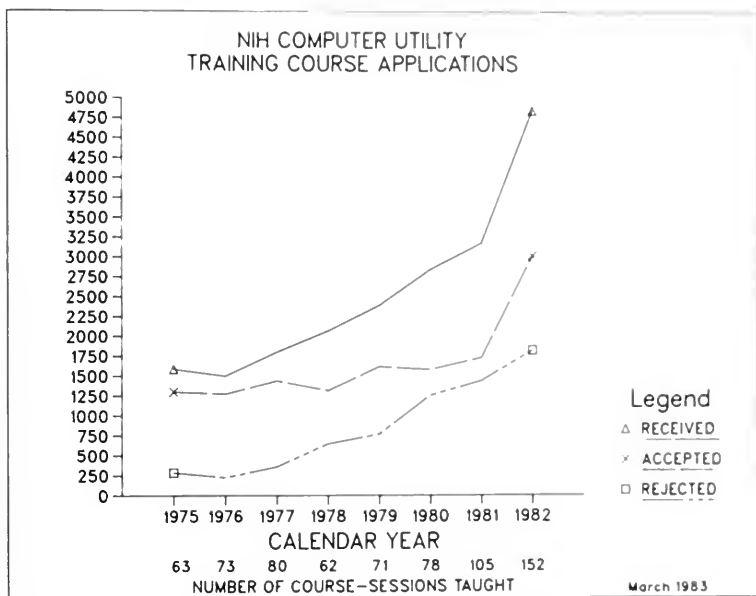
A variety of programming languages are available on the NIH Computer Utility. Languages like FORTRAN, COBOL, PASCAL, BASIC, Assembler, PL/I, SAIL, and SPEAKEASY provide for a wide range of applications in a variety of different research and management areas. There is also a data base/data management system (IMS), the TELL-A-GRAF interactive graphics package, and a comprehensive library of statistical and utility programs. Online computing and batch job submission are available interactively on the IBM System 370 through WYLBUR and TSO, and through timesharing services on the DECsystem-10. Devices for job output on paper and microfiche are available, and there are programs for creating two-dimensional or three-dimensional graphics displays for advanced research projects.

Users of the Computer Utility are informed of current programming standards and available facilities through two comprehensive manuals, the *Computer Center Users Guide* and the *DECsystem-10 Timesharing Guide*. Changes in the Utility are announced to users through *INTERFACE*, a periodic technical newsletter. An in-house training program conducted 152 formal classroom lecture courses to over 3,000 students and a variety of multimedia self-study courses to help users develop expertise in the use of the Utility this year.

Highlights of the Year's Accomplishments

The most exciting accomplishment of FY83 was a dramatic increase in the amount of system resources available to user programs. Requested for several years by many of the Utility's users, the expanded resource limits were made possible largely by last year's upgrade of all IBM System 370 hardware.

A number of areas were affected by the expansion of system resources. Processor time allowed was increased 50 percent for all job classes, except class 'E,' which was increased 87 percent. The maximum REGION size available to all batch jobs and TSO sessions was increased to two million bytes, thus allowing greater flexibility for large data set processing



or matrix manipulation activities. In addition, the maximum size of data sets eligible for storage on the MSS was more than doubled, the amount of DASD scratch space available to each job step was increased 100 percent to 475 million bytes, and the limit for online printed output was raised by a factor of four to 20,000 lines.

These expanded resource limits, which represent the most comprehensive increase in resources ever offered by the Utility, will improve system efficiency and cost effectiveness while providing greater flexibility and convenience in the design and processing of user programs, particularly for large data sets.

An entirely new system of self-study, Independent Training Assisted by Computer (ABC), was introduced this year in response to users' ever-growing need for computer-related training. Designed and developed by the Computer Center, ABC courses allow users to study from a printed text, from a computer terminal, or

from a combination of both. ABC courses give users the option of taking either an entire course or only selected parts of the material; lessons may be repeated as often as desired and can be studied at any convenient location. 'Introduction to WYLBUR' was the first ABC course made available.

Because of the widespread and growing use of microcomputers and other 'intelligent' devices at NIH, a major policy decision to develop facilities that will make the resources and services of the Computer Utility available to microcomputer users was announced this year. A facility was introduced to allow microcomputers to be used as terminals to access the Utility, and a function to permit programs and data to be transferred between the various microcomputers and the Utility was tested and installed. An entirely new communications service, called SNA/SDLC 3270, was introduced on the IBM system in order to give a wider range of devices dial-up access to the Utility.

NIH COMPUTER UTILITY FY83 RATE REDUCTIONS

Service	Rate		Percent Reduction
	FY82	FY83	
Terminal Rental:			
NIH7000/month	\$176.00	\$120.00	31.8
Data Storage (online):			
Public/track	.03	.025	16.7
Dedicated/track	.015	.0125	16.7
MSS/megabyte	3.07	2.55	16.9
Processing:			
BATCH/resource hour	\$ 26.40	\$ 22.20	15.9
WYLBUR/second	.97	.72	25.8
TSO/second	1.90	1.20	36.8
IMS/transaction	.20	.18	10.0
Printing/1000 lines	.87	.64	26.4
Discount Processing	50%	40%	20.0

Users of the NIH Computer Utility saved over 7 million dollars when the largest rate reduction ever offered by the NIH Computer Center became effective on February 1, 1983. These savings were compounded on July 1, 1983 when rates for interactive services on the IBM System 370 were reduced even further. The combined reductions ranged from 10 to 62 percent including significant decreases in almost all areas of batch and interactive processing, data storage and terminal rental.

This is the 16th consecutive year that the NIH Computer Center has been able to pass on savings to users in the form of rate reductions. Overall, rates have decreased 87.3 percent, from 175 dollars per resource hour in 1968 to slightly over 22 dollars in 1983.

The installation of new, more cost-effective hardware last year--together with the efforts of Computer Center staff to improve the internal operating efficiency of the system--has contributed significantly to reducing operating overhead. The constantly-increasing demand for computational services is another important factor that makes continually decreasing rates possible. The fixed costs and overhead of the system do not increase in direct proportion to its processing capacity; and, because the Utility operates as a zero balance, cost-recovery facility, all savings resulting from improved financial performance are returned to users in the form of lower rates for services. Therefore, the expansion of the system actually works to reduce per unit costs for all users. This 'economy of scale' is one of the major advantages of the Computer Utility concept as implemented at NIH.

A major accomplishment of the past year was the development of a multiphased plan to provide complete data set security for the over 300,000 data sets stored on the NIH Computer Utility. The new security plan, which utilizes IBM's Resource Access Control Facility (RACF), will enable users, at their option, to control access to individual data sets or groups of data sets from WYLBUR, TSO, and batch jobs. The RACF security system allows users to: limit access to sensitive information to authorized users, prevent deliberate or accidental destruction of data by unauthorized users, and centralize access control to data sets processed by multiple users.

Software additions and system enhancements introduced during the year focused heavily on graphics. GRAPH1, a new program for drawing graphs, became available on the DECsystem-10. A graphics package was added to the interactive language SPEAKEASY, and color graphics capabilities were introduced on OMNIGRAPH. The International Mathematical and Statistical Library underwent a major upgrade, and a facility was added for users to obtain current status information about online data sets and tape volumes through the terminal.

Future Plans

Developing support facilities to encourage maximum utilization of the Computer Utility will be a major priority of the coming year.

Recognizing the importance of the microcomputer and other 'intelligent' microprocessor-based devices at NIH, the Computer Center will continue to explore ways to develop the potential of these powerful and versatile tools. Because of the vast variety of microprocessors available and the almost limitless array of associated software, a great deal of planning and coordination will be necessary to insure long-term compatibility and maximum effectiveness. Emphasis will be placed on researching and implementing additional functions and facilities to enable microcomputer users to take full advantage of the resources and services available from the Computer Utility.

Expansion of training opportunities for Computer Utility users, a continuing goal of the Computer Center, will be particularly important next year. A number of additional ABC independent training courses will be developed and implemented, while full support is continued for classroom training and self-study courses.

The coming year will see the completion of a total security environment that is functional as well as convenient. The overall security plan will encompass physical security, computer room access, and control of output distribution, as well as effective data set protection.

In keeping with the growing demand for more sophisticated computer graphics, development of enhanced graphic output facilities and display mathematics capabilities will be an important priority next year. In addition, all standard terminals used at NIH will be replaced with state-of-the-art equipment that has increased display capabilities.

New interactive display terminals will replace the NIH7000 editing display terminals. Designated the NIH8188, the new terminal will display 132 characters per line, have twice as many function keys and four times the memory capacity of the NIH7000. Replacements for the CT45 hard copy terminal and the T1222 high-speed hard copy terminal will be selected through the competitive procurement process.

A foil printing utility that will allow users to generate high quality overhead transparencies is being planned in response to user requests. A number of enhancements to WYLBUR, many suggested by the user community, will be implemented, and the Computer Center staff will continue to investigate and evaluate currently available software offerings to determine which might be beneficial to users of the NIH Computer Utility.

Publications

McLaughlin, B. An experimental Comparison of Discovery and Didactic Computerized Instructional Strategies in the Learning of Computer Programming '83 National Educational Computing Conference, Baltimore, MD, June 6-8, 1983

MATHEMATICAL ANALYSIS BIOLOGICAL PHENOMENA
MISTRY THEORETICAL ANALYSIS CELL LOCOMOTION
SE LASER LIGHT SCATTERING BIOCHEMISTRY CHEMISTRY
ROBABILITY DENSITY FUNCTION MOLECULAR FORMULAS
EL SCRYTALLOGRAPHIC DATA KINETICS HYDRATION
COMPUTER-BASED STUDIES MATHEMATICAL THEORY
PUTINGS SINGULAR VALUE DECOMPOSITION DATA
MATHEMATICS MEDICAL APPLICATIONS STATISTICS
H RECOGNITION IMAGE PROCESSING BIOMEDICAL
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Office of the Director

Arnold W. Pratt, Director

Function and Scope of Work

The Office of the Director provides overall program and management direction for DCRT. It includes an Equal Employment Opportunity Office and three offices whose activities supplement the work of the DCRT laboratories and branches:

- The Office of ADP Policy Coordination (OADPPC) is the central NIH focus for advice and assistance on matters related to the complex ADP policy and procedures governing the procurement and management of computers in the Federal government. It serves as the point of contact on these matters with other parts of DHHS and other Federal agencies.
- The Office of Administrative Management (OAM) provides general administrative and managerial support for the work of DCRT.
- The Office of Scientific and Technical Communication (OSTC), including the DCRT Information Office and the DCRT Library, serves as a central source of information about DCRT activities and about computing and related disciplines.

In addition, the Office of the Director sponsors a number of individual research and development projects.

FY83 Highlights

This year, the DCRT Equal Employment Opportunity Office developed the Division's first Affirmative Action Program/Federal Equal Opportunity Recruitment Program plans.

A major change took place in the Office of ADP Policy Coordination. At the end of FY82 OADPPC Chief Mr. Henry Juenemann retired, after experience spanning two decades of dynamic and complex development of computing at NIH.

In early FY83 two branches of the NIH Division of Management Policy (DMP) were transferred to DCRT because their work related to computer-based systems. The personnel and responsibilities of the Systems Policy and Planning Branch and the Systems Approval,

Review, and Coordination Branch were placed in the OADPPC.

The functions of these branches while in DMP included keeping an inventory of NIH software systems, clearing new administrative systems and reviewing existing systems, and serving as the NIH System Security Office. Integration of these functions with those of OADPPC will result in more effective support for the NIH scientists and managers who rely on DCRT for help on matters related to ADP policies and procedures.

The Office of Administrative Management again handled the broad range of personnel, budget, accounting, and general administrative functions that occur in a complex NIH research and service division of 320 people with a total budget over 40 million dollars. Although there were no major changes during the year, these activities continued to increase in volume and complexity.

For example, the Project Control Office in the DCRT Financial Management Office coped with a 15 percent increase in the number of registered users of the NIH Computer Center. At year's end there were some 12,000 users on almost 3,000 accounts. They also participated in the NIH implementation of new billing procedures (SIBAC) to facilitate interagency payments across the Federal government.

The DCRT Personnel Office handled the increased activity that followed a relaxation of most hiring restrictions by the Department and PHS without any substantial decrease in the complexity of hiring new personnel from OPM registers. The office also carried the responsibility for reviewing all of the paperwork associated with the first year of implementing the new departmental Employee Performance Management System.

In addition to overseeing the Division's administrative functions, the DCRT Executive Officer served the Division as its International Representative to the Fogarty International Center, its Legislative Contact, and its Program Planning Officer in liaison with the NIH Office of Program Planning and Evaluation.

The DCRT Library continued to serve an active community of users throughout NIH as well as within DCRT. In general there was a ten to thirty percent increase in such measures of use as books circulated, new users registered, and interlibrary loans requested from the library. The Librarian completed her work on the executive boards of the District of Columbia Library Association and the national OCLC Users Council but replaced these activities with work on the D.C. Chapter of the Special Library Association. The Library staff pursued a long term interest in computer systems to serve small libraries, in the expectation that the advent of small computers and commercial software will make this important in the coming year.

The Information Office encountered a 20 percent increase in the demand for publications describing the work of DCRT, and it responded to many special requests for assistance and information from DCRT staff and from people outside of DCRT and NIH. The Office completed work on its computerized file of citations to the hundreds of scientific papers written and presentations given by the DCRT staff over the last 15 years.

Among the projects sponsored by the Office of the Director, the Personal Workstation Project received great attention within the Division and other parts of NIH. In mid-FY83 the Director organized a core group of computer experts from several DCRT laboratories and branches to actively explore the effective use of personal computers as workstations in laboratories and offices throughout NIH. The initial work of the group centered on an examination of the IBM Personal Computer and the many hardware and software products that vendors have recently announced to support and extend this basic personal computer architecture.

Future Plans/Trends

Much of the work in the coming year will be a direct continuation of that carried out in FY83 and previous years to meet the needs of both the DCRT staff and the growing community of people within NIH who use

or are interested in using computers to support their work.

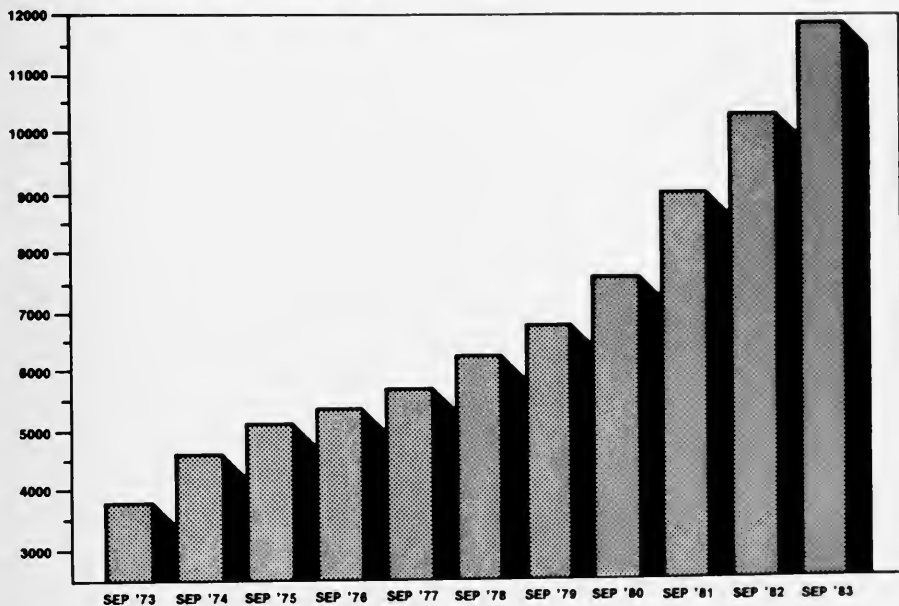
The reallocation of functions within the OADPCC and other parts of the Office of the Director should enhance the ability of DCRT to carry out its policy, planning, and system review activities.

The Personal Workstation Project will extend to other parts of the Division. Members of all DCRT laboratories and branches will serve as the testing ground for hardware and software components that can be of use to others at NIH.

Publications and Presentations

- Brenner, S.L., and Korn, E.D.: AMP and ADP Inhibit ATP Hydrolysis by F-actin at Steady State But Have No Effect During Polymerization. Twenty-seventh Annual Meeting of the Biophysical Society, San Diego, CA, February 13-16, 1983.
- Brenner, S.L., and Korn, E.D.: On the Mechanism of Actin Monomer-Polymer Subunit Exchange at Steady State. *Journal of Biological Chemistry* (in press).
- Brenner, S.L., Tobacman, L.S., and Korn, E.D.: The Kinetics of Actin Polymerization and Monomer-Polymer Exchange at Steady State. *Proceedings of the IUB Symposium*. Sydney, Australia, August, 1982 (in press).
- Division of Computer Research and Technology Fiscal Year 1982 Annual Report, Volume 1, October 1982, 38 pp.
- Division of Computer Research and Technology Fiscal Year 1982 Annual Report, Volume 2, October 1982, 96 pp.
- Dwyer, A.J., Gleubiger, D., Ecker, J.G., Doppman, J.L., Prewitt, J.M.S., and Plunkett, J.: The Radiographic Followup of Patients with Ewing Sarcoma: A Demonstration of a General Method. *Radiology* 145: 327-331, 1982.
- Dwyer, A.J., Prewitt, J.M.S., Ecker, J.G., and Plunkett, J.: The Use of Hazard Rate to Allay the Peril of Inappropriate Followup: An Optimization Approach to Patient Management. *Journal of Medical Decision Making* (in press).
- Kroop, D.O., and Prewitt, J.M.S.: Privacy in Medical Information Systems: Threats and Countermeasures. MEDCOMP '82, Philadelphia, PA, September 23-25, 1982.
- Nalcioğlu, O., and Prewitt, J.M.S. (Eds.): *Proceedings of the International Workshop on Physics and Engineering in Medical Imaging* (in press).
- Prewitt, J.M.S.: Pattern Recognition Frontiers in Medical Imaging. Harvard University Information Technology Colloquium Series, March 17, 1983.
- Prewitt, J.M.S., Shao, J.X., Bahr, G.F., Lipkin, L.E., and Lemkin, P.: Computer Analysis of Myelinated Nerve Tissue. Fourth International Conference on Automation of Diagnostic Cytology, Montreal, Canada, June 24-25, 1983.
- Ranft, U., Fu, K.S., and Prewitt, J.M.S.: Segmentation of Microscopic Transverse Section Pictures of Muscle Tissue Using Split-and-Merge Technique. *Proceedings of the 6th International Conference on Pattern Recognition*, October 1982, pp. 626-628.
- Ranft, U., Fu, K.S., and Prewitt, J.M.S.: Segmentation of Transverse Section Pictures of Muscle Tissue. World Congress on Medical Physics and Biomedical Engineering, Hamburg, Germany, September 7-9, 1982.
- Schuettle, S.E., Shackney, S.E., Smith, C.E., and Prewitt, J.M.S.: An Iterative Method for the Decomposition of Gaussian Distortions From DNA Histograms. MEDCOMP '82, Philadelphia, PA, September 23-25, 1982.

Registered Users of the NIH Computer Utility



The Project Control Office processes requests for new accounts, registers new users, and prepares monthly billing data for the NIH Computer Utility.

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DISCRIMINATION PROHIBITED: Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the Division of Computer Research and Technology must be operated in compliance with these laws and Executive Orders.



Division of Computer Research and Technology
National Institutes of Health
Bethesda, Maryland 20205

Division of Computer Research and Technology

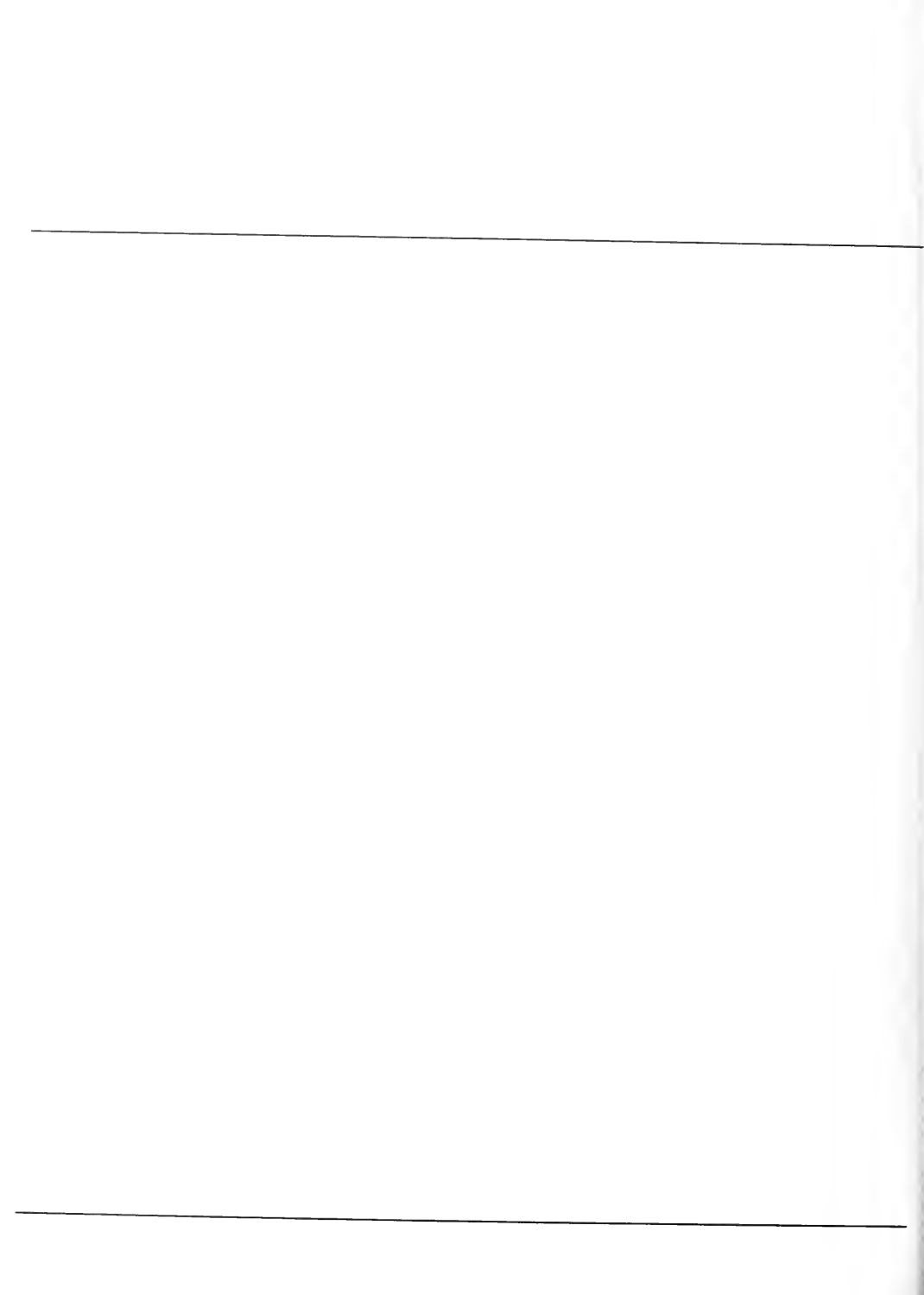
Fiscal Year 1983

Annual Report

Volume 2

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

MATHEMATICAL ANALYSIS BIOLOGICAL PHENOMENA
MISTRY THEORETICAL ANALYSIS CELL LOCOMOTION
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ROBABILITY DENSITY FUNCTION MOLECULAR FORCE
ELSCRYTALLOGRAPHIC DATA KINETICS HYDRATION
COMPUTER-BASED STUDIES MATHEMATICAL THEORETICAL
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MATHEMATICS MEDICAL APPLICATIONS STATISTICS
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OCUMENTATION CENTRAL COMPUTER UTILITY FEEDBACK
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SCIENTIFIC AND TECHNICAL COMMUNICATION ADMINISTRATION
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UBLICATIONS COMPUTERIZED BIBLIOGRAPHY SEARCH
EEO PERSONAL COMPUTERS SYSTEMS POLICY AND MANAGEMENT
ND COORDINATION FOR PLAN MANAGERIAL FUNCTIONS



Division of
Computer
Research and
Technology

Fiscal Year 1983
Annual Report
Volume 2

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

MATHEMATICAL ANALYSIS BIOLOGICAL SCIENCE
MISTRY THEORETICAL ANALYSIS
SES LASER LIGHT SCATTERING
ROBABILITY DENSITY FUNCTION
ELSCRYTALLOGRAPHIC DATA
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N RECOGNITION & GEOMETRIC MEDICAL
ESPARTIAL DIFFERENTIAL EQUATION
PROGRAMS PACKAGE STATISTICAL
MLAB CURVE-FITTING NUMERICAL DERIVATIVES
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ATOR PACKAGE GRAPHICAL DISPLAY LINGUISTIC
EDICAL LANGUAGE SYSTEM ANALYSIS DISCRETE
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EEO PERSONAL COMPUTERS SYSTEMS POLICY AND
ND COORDINATION FOR PLAN MANAGERIAL FUN



Foreword

The Division of Computer Research and Technology has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH. DCRT serves as a scientific and technological resource for other parts of PHS, and for other Federal organizations with biomedical and statistical computing needs.

DCRT programs focus on three primary activities: conducting research, developing computer systems, and providing computer facilities.

The fiscal year 1983 annual report describes our work in two volumes:

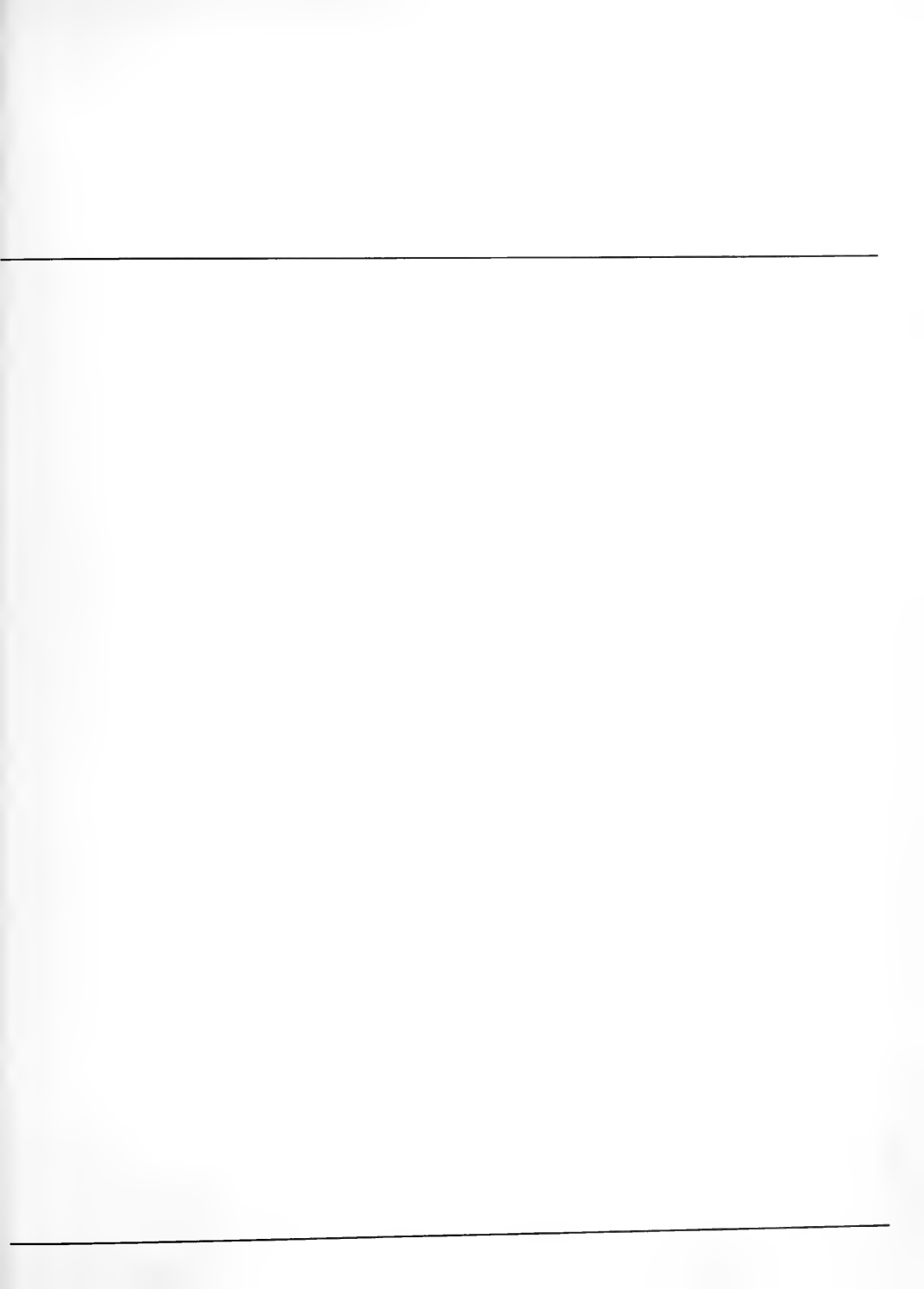
Volume 1 gives an overview of the work of each group, highlighting the year's accomplishments;

Volume 2 gives details about the projects and activities of each group.

Contents

Physical Sciences Laboratory	1	Analysis of Coupled Transport and Biochemical Kinetics.....	20
Consulting Services.....	1	Mathematical and Computational Methods for Solving Nonlinear Equations.....	22
Theory of Biochemical Separation Techniques.....	2	Numerical Approximation Techniques for the Solution of Reaction-Diffusion Systems in Biology	23
Studies in Mathematics and Statistics.....	2	Laboratory of Statistical and Mathematical Methodology.....	25
Correlation Function Spectroscopy/Laser Light Scattering	3	Automated Data Processing of Medical Language	28
Cell Motility and Chemotaxis	3	Cluster Analysis.....	29
Molecular Forces in Cellular Assembly	4	Research Topics in Computer Science	29
Computerized Typesetting of Scientific Papers.....	4	Discrete Mathematics and Applications	30
Quantitative Analysis of Cell Structure, Membranes and Organ Development	5	Multivariate Statistical Analysis	31
Diffusion of Molecules on Cell Surfaces and Light Scattering from Fluids	6	Linear Methods in Statistics.....	31
Effect of Solvent on Biological Macromolecules.....	6	Nonnumerical Programming Techniques and Applications.....	32
Laboratory of Applied Studies	9	Topics in Geometry and Analysis	32
Computer-based Studies of Physiology and Pathophysiology During Exercise.....	11	Nonparametric Statistics	33
Computer Based Method of Monitoring the CNS in Critically Ill Patients.....	12	Computer Systems Laboratory	35
Computer Systems for Nuclear Medicine.....	13	Computer Support for Flow Cytometry/ Electronic Cell Sorting (FC/ECS).....	40
Computer-Aided Analysis of Electrocardiograms	14	Cardiac Scintillation Probe	41
Statistical Research in Clinical Pathology	15	Medical Intensive Care Unit Patient Monitoring Computer System	43
Computer based analysis and image processing in electron microscopy and x-ray and electron-loss spectroscopy.....	16	Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies.....	44
Investigation of Hybrid Computing for the Analysis of Physiologic Signals.....	17	Computer Assisted Tomography (CAT) Scan Image Analysis in Aging Studies	45
Mathematical Models of Binding Equilibria ..	17	Robust Boundary Detection of Necturus Gall Bladder Cells	46
Mathematical Modeling of Substrate Transport in Physiological Environments.....	18	Rehabilitation Medicine Department Computer System.....	47
Network Modeling in Biology	19	Aging Studies Image Analysis System.....	48

Positron Emission Tomography (PET) Facility	49	Distributed Laboratory Data Acquisition and Control System	64
Picture Archiving and Communication System	49	Personal Computers in Laboratory Applications	66
Automated Management of Critically Ill Patients	50	Image Processing Facility	66
Computer Interfaces for Clinical Laboratory Instruments	51	Medical Image Data Compression	67
Automated Pulmonary Physiology Testing ... 52		Analytic Models of Computer System Performance	68
Anesthesia Computer System	54	Verbal Access to Computers for the Blind	69
Medical Information Technology Project	55	Data Management Branch	71
Molecular Graphics, Computer Modeling, and Sequence Analysis	56	Computer Center Branch	79
Computer Analysis of Gel Electrophoresis ... 57		Design and Development of an Advanced Molecular Graphics Facility	80
Morphometric Analysis of Normal and Neoplastic Tissue Cultures	58	Office of the Director	83
Virus Structure As Determined by Image Processing of Electron Micrographs	58	Personal Computer Workstations	83
Image Processing of Electron Micrographs .. 59		Concordance Program	83
Electron Microanalysis Facility	60	A Program for Finding Noun Phrases in English Text	84
Molecular Interactions Laboratory Data System	62	Actin Assembly in Nonmuscle Cells	84
Californium-252 Plasma Desorption Mass Spectrometer Data System	63	Molecular modeling of the structure of carbohydrates	85
		Reprint File Index	85



**MATHEMATICAL ANALYSIS BIOLOGICAL PHENOMENA
MISTRY THEORETICAL ANALYSIS CELL LOCOMOTION
SES LASER LIGHT SCATTERING BIOCHEMISTRY CHEMISTRY
ROBABILITY DENSITY FUNCTION MOLECULAR FORCE
EL SCRY TALLOGRAPHIC DATA KINETIC SHYDRATION**

Physical Sciences Laboratory

George H. Weiss, Chief

Summary of Activities

Consulting Services. George H. Weiss (PSL). PSL provides consulting services to NIH researchers in problems relating to the physical sciences, applied mathematics, and statistics.

Theory of Biochemical Separation Techniques. George H. Weiss (PSL). Several results were obtained for the solution of partial differential equations describing chromatographic systems with random mobilities. These are necessarily approximate, making use of the method of averaging. They appear to contradict the conjectured Gaussian shape of the peaks of isolated species in ideal columns.

Studies in Mathematics and Statistics. George H. Weiss (PSL). Several projects have been undertaken on the application of random walk methods in the determination of crystallographic structures. These methods allow the experimenter to distinguish between different space groups using available data. The general problem of fitting a probability density function using moments also has been studied with particular application to crystallography, but with a wider area of possible use.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph Nossal (PSL). Considerable time on this project was devoted to the application of light scattering techniques to problems arising in other work by NIH scientists. For example, a combination of light scattering and ultracentrifugation has been used to characterize the heterogeneity of coated vesicles from brain tissue.

Molecular Forces in Cellular Assembly. Adrian Parsegian (PSL). The technique developed for measuring the force between DNA helices in solution has been successfully applied to find the pressure needed to pack DNA into a viral head.

Effect of Solvent on the Properties of Biological Macromolecules. B. Lee (PSL). This study is made using statistical mechanical techniques. We have shown, for example, that a protein molecule "breathes" in aqueous solution and that the extent of this breathing motion is directly related to the repulsion between protein and water molecules.

Quantitative Analysis of Cell Structure, Membranes, and Organ Development. Nahum Gershon (PSL). This project is directed towards image reconstruction from electron micrographs of cells taken at the University of Colorado and NICHD. A computer system has been assembled, and software is being written for manipulation of the digitized images.

Research Projects

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		201 CT00027-16 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)		
Consulting Services		
PRINCIPAL INVESTIGATOR (and other professional personnel on subsequent pages)		
(Name, title, laboratory and institute affiliation)		
George H. Weiss, Ph.D., Chief, PSL, DCRT		
COOPERATING UNITS (if any)		
J. S. Kieley, PSL, DCRT; R. J. Nossal, Ph.D., PSL, DCRT; R. A. Brooks, SN, NINCOS; J. A. Ferretti, IR CH, NHLBI; J. L. Aron, C DCCP B, NCI; A. Stabo, A LCP, NIADK		
LABORATORY		
Physical Sciences Laboratory		
SECTION		
INSTITUTE AND LOCATION		
Division of Computer Research and Technology		
TOTAL MANTEARS	PROFESSIONAL	OTHER
1.0	0.9	0.1

Consulting Services

Consulting services are provided to NIH researchers in a variety of disciplines including physics, applied mathematics, and statistics. A theory has been developed for the calculation of sampling errors in kinetics experiments. Two variants of the theory have been applied, one to parameters measured in the use of positron emission tomography, and the second to errors incurred in Fourier transform NMR spectroscopy. In the first of these applications the techniques allow estimation of experimental error from available data, but will also furnish a means of optimizing the use of PET scanners. In the second, we have compared the accuracy and precision of peak area estimates obtained by curve fitting and numerical integration from FT NMR data. Both methods are currently used by NMR spectroscopists, but our analysis showed that curve fitting is far superior to numerical integration.

A joint study of the validity of the Wilemski-Fixman approximation for calculations of rates in polymer

physics is presently underway with A. Szabo. Calculations with an exactly solvable model allow us to estimate the limits of validity of this model, and integral equation methods have suggested more accurate alternatives to the much used approximation.

Together with J. Aron we have developed a mathematical model of the kinetics of diseases with superinfection.

A joint project has been initiated on the understanding of the kinetics of diffusion-controlled reactions. Approximate techniques for the solution of such problems in polymer physics have been in the literature for many years. An application of infinite order perturbation theory techniques has led to an understanding of limitations on present approximations and to improvements in the calculation of rates.

Publications:

- Stone, M., Sonies, B. C., Shawker, T. H., Weiss, G. H., and Nadel, L.: Analysis of realtime ultrasound images of tongue configuration using a grid-digitizing system. *J. Phonetics* (in press).
- Weiss, G. H., Caveness, W. F., Einsiedel-Lechtape, H., and McNeel, M. L.: Life expectancy and causes of death in a group of head-injured veterans of World War I. *Arch. Neurol.* 39: 741-743, 1982.
- Weiss, G. H., Feeney, D. M., Caveness, W. F., Dillon, D., Kistler, J. P., Mohr, J. P., and Rish, B. L.: Prognostic factors for the occurrence of posttraumatic epilepsy. *Arch. Neurol.* 40: 7-10, 1983.
- Weiss, G. H., Ferretti, J. A., Kiefer, J. E., and Jacobson, L.: A method for eliminating errors due to phase imperfection in NOE measurements. *J. Mag. Res.* (in press).
- Weiss, G. H., and Rice, J. A.: A combinatorial problem in pharmacology. *J. Math. Biol.* 14: 195-201, 1982.
- Weiss, G. H., and Szabo, A.: First passage problems for a class of master equations with separable kernels. *Physica* (in press).
- Weiss, G. H., Talbert, A., and Brooks, R. A.: The use of phantom views to reduce CT streaks due to insufficient angular sampling. *Phys. in Biol. and Med.* 27: 1151-1162, 1982.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00014-16 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Theory of Biochemical Separation Techniques		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) George H. Weiss, Ph.D., Chief, PSL, DCR		
COOPERATING UNITS (if any) S. West, Ph. D., La Jolla Institute, La Jolla, CA		
LAB/BRANCH Physical Sciences Laboratory		
SECTION		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MANYEARS: 0.1	PROFESSIONAL: 0.1	OTHER: 0.0

Theory of Biochemical Separation Techniques

Mathematical techniques are developed and applied to the design and analysis of biochemical separation experiments. The study of chromatographic systems with randomly varying mobilities has been initiated partly verifying and partly contradicting speculations about the effects of random parameters that have appeared in the literature.

Publications:

- Weiss, G. H.: Chromatographic kinetics and the phenomenon of tailing. *Sep. Sci. & Tech.* 17:1609-1622, 1982.
- Weiss, G. H., and Rice, J.: Optimal parameters for the measurement of the half-width of a Gaussian peak. *Sep. Sci. & Tech.* 17: 1101-1115, 1982.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00024-08 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Studies in Mathematics and Statistics		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) George H. Weiss, Ph.D., Chief, PSL, DCR		
COOPERATING UNITS (if any) J. E. Kiefer, PSL, DCR; R. J. Rubin, Ph.D., Sr. Scientist, NBS; K. E. Shuler, Ph.D., and K. Lindenberg, Ph.D., U. of California, San Diego; U. Shmueli, Ph.D., Tel-Aviv University, Israel; A. J. C. Wilson, Ph.D., Cambridge University		
LAB/BRANCH Physical Sciences Laboratory		
SECTION		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MANYEARS: 0.8	PROFESSIONAL: 0.6	OTHER: 0.2

Studies in Mathematics and Statistics

We have analyzed several aspects of Pearson random walks that are useful in determining the space groups

of molecules from crystallographic data. In particular, an exact expression has been found for the probability density of the projection of a Pearson random walk near maximum extension. Useful numerical methods have been developed for calculating the projection density as well as the end-to-end density for Pearson random walks with one or two outstandingly long steps included among a larger number of smaller steps.

Publications:

- Kiefer, J. E., and Weiss, G. H.: The Pearson random walk. *AIP Proceedings* (in press).
- Rubin, R. J., and Weiss, G. H.: Limiting thickness of an adsorbed polymer chain. *J. Chem. Phys.* 78: 2039-2043, 1983.
- Weiss, G. H.: Random walks and their applications. *Am. Sci.* 71: 65-71, 1983.
- Weiss, G. H.: Random walks. *Encycl. Stat. Sci.* (in press).
- Weiss, G. H., and Kiefer, J. E.: The Pearson random walk with unequal step sizes. *J. Phys. A: Math. Gen.* 16: 489-495, 1983.
- Weiss, G. H., and Rubin, R. J. (Eds.): Proceedings of the Symposium on Random Walks. *J. Stat. Phys.* 30: 249-561, 1983.
- Weiss, G. H., and Rubin, R. J.: Random walks: theory and selected applications. *Adv. Chem. Phys.* 52: 363-505, 1983.
- Weiss, G. H., Shuler, K. E., and Lindenberg, K.: Order statistics for first passage times in diffusion processes. *J. Stat. Phys.* 31:255-278, 1983.

studies concern the development of shear rigidity in plasma clots, the relationship between molecular structure and the mechanical properties of polyacrylamide gels, and the effects of calcium ions on the conformations of mucin glycoproteins.

Assistance has been given to other research projects for which it has been important to obtain information about the size of particles in laboratory samples. Notable among these is an investigation of the efficacy of protocols for preparing "coated vesicles" from brain tissue (cf. project Z01 CT 00022-16 PSL). Also, we continue to provide supporting services for the development of laser Doppler bloodflow instrumentation and other devices utilizing quasi-elastic light scattering.

Publications:

- Gladner, J. A., and Nossal, R.: Effects of crosslinking on the rigidity and proteolytic susceptibility of human fibrin clots. *Thrombosis Res.* 30:273-278, 1983.
- Nossal, R., and Jolly, M.: Shear waves and internal viscosity in cylindrical gels. *J. Appl. Phys.* 53:5518-5525, 1982.
- Nossal, R., Weiss, G. H., Nandi, P. K., Lippoldt, R. E., and Edelhofer, H.: Sizes and mass distribution of clathrin coated vesicles from bovine brain. *Arch. Biochem. Biophys.* (in press).
- Steiner, C. A., Litt, M., and Nossal, R.: Applications of dynamic light scattering to studies of mucin structure. *Proceedings of 1983 Symposium on New Techniques in Bioreology* (in press).
- Steiner, C. A., Litt, M., and Nossal, R.: Effects of calcium ions on the structure of canine tracheal mucin. *Bioreology* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00021-12 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Correlation Function Spectroscopy/Laser Light Scattering		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Ralph J. Nossal, Ph.D., Research Physicist, PSL, DCRT		
COOPERATING UNITS (If any) K. Bonner, Ph.D., &CIB, DRS; N. Edelhofer, Ph.D., CT, NIADDK; J. Gladner, Ph.D., USC, NIADDK; M. Litt, Ph.D., Dept. Chem. Eng., Univ. Pennsylvania; C. A. Steiner, Ph.D., Dept. Chem. Eng., Univ. PA; G. H. Weiss, PSL, DCRT.		
LAB BRANCH Physical Sciences Laboratory		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MANYEARS	PROFESSIONAL	OTHER
0.9	0.8	0.1

Correlation Function Spectroscopy/Laser Light Scattering

Several studies involving dynamic light scattering techniques have been undertaken in collaboration with scientists at NIH and other research institutions. Recent emphasis has been on developing methods to study the properties of large lattice-like polymer structures. These techniques have been applied, for example, to an examination of fibrin gels and plasma clots in order to assess the effects of subunit crosslinking on the resistance of a clot to proteolytic degradation. Other

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00017-11 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Cell Motility and Chemotaxis		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Ralph J. Nossal, Ph.D., Research Physicist, PSL, DCRT		
COOPERATING UNITS (If any)		
LAB BRANCH Physical Sciences Laboratory		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MANYEARS	PROFESSIONAL	OTHER
0.2	0.2	0.0

Cell Motility and Chemotaxis

Theoretical and experimental analyses of various aspects of cell locomotion have been undertaken over the past few years. These have included formulation of mathematical descriptions of the macroscopic response

that moving cells show in response to chemical stimuli in order to understand the relationships between the net movements of a population of cells and the underlying stochastic motile behavior of individual cells within that population. Such information is useful in interpreting the results of in vitro assays for leukocyte chemotaxis. Other aspects of this project include development of laser light scattering techniques for measuring the motility of flagellated bacteria and other swimming microorganisms. We also have been concerned with devising dynamic light scattering schemes for probing the mechanical properties of cytoplasmic gels. Current emphasis is on formulating mathematical descriptions of the sequence of biophysical phenomena involved in the transduction of information about chemical gradients into the locomotory response of chemotactic bacteria.

Publications:

Nossal, R.: Stochastic aspects of biological locomotion. *J. Stat. Phys.* 30:391-400, 1983.

measurements show qualitative differences from popular theories adds to the interest in our findings.

Studies on bilayer membrane interaction have revealed the importance of these forces in bilayer deformation and uncovered conceptual difficulties associated with models of cell membrane fusion.

In all these systems the paramount role of "hydration" forces, first identified by Parsegian and Rand, is evident. The primacy of hydration factors is emerging as a theme of molecular assembly in cellular and subcellular systems.

Publications:

Gruen, D. W. R., Marcelja, S., and Parsegian, V. A.: Water structure near the membrane surface. In Perelson, A. (Ed.): *Membrane Surfaces*. New York, Marcel Dekker (in press).

Loosley-Millman, M. E., Rand, R. P., and Parsegian, V. A.: Effects of monovalent ion binding and screening on measured electrostatic forces between charged phospholipid bilayers. *Biophys. J.* 40:221-232, 1982.

Parsegian, V. A.: Dimensions of the "intermediate" phase of dipalmitoylphosphatidylcholine. *Biophys. J.* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00026-08 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Molecular Forces in Cellular Assembly		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) V. Adrian Parsegian, Ph.D., Research Physicist, PSL, DCRT		
COOPERATING UNITS (if any) B.-K. Lee, Ph.D., PSL, DCRT; D. Rau, Ph.D., NIADGK; R. F. Rand, Ph.D., and W. Poller, Ph.D., Brock Univ., Canada; L. J. Lis, Ph.D., Ill. Inst. Tech., Chicago, Ill.; E. A. Evans, Ph.D., U. British Columbia, Canada; J. Z. Zimmerberg, M.D., Ph.D., PSL, DCRT; S. White, Ph.D., U. CA, Irvine (PSL 1983)		
LABORATORY Physical Sciences Laboratory		
SECTION		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MANYEARS	PROFESSIONAL	OTHER
0.9	0.8	0.1

Molecular Forces in Cellular Assembly

After achieving a direct measurement of forces between DNA double helices in solution last year, we have systematically investigated the determination of that force by the ionic species bound to the molecular surface. An especially exciting byproduct of our investigation was the realization that DNA in bacteriophage heads is under conditions similar to those under which we made our measurements. We have thus determined the long sought "DNA pressure" of packing the viral head. The fact that our

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00066-04 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Computerized Typesetting of Scientific Papers		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) V. Adrian Parsegian, Ph.D., Research Physicist, PSL, DCRT		
COOPERATING UNITS (if any) N. Crawford, PSL, DCRT; N. McNeel, Computer Systems Analyst, PSL, DCRT; M. Douglas, Computer Systems Analyst, LAS, DCRT; M. Horton, Computer Systems Analyst, LAS, DCRT; Rockefeller University Press, Science Press, Biophysical Society		
LABORATORY Physical Sciences Laboratory		
SECTION		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MANYEARS	PROFESSIONAL	OTHER
0.6	0.3	0.3

Computerized Typesetting of Scientific Papers

During the current year this project has enjoyed good practical progress toward achieving its objective of converting word processor output to a typeset page in a scientific journal. There has been a shift in emphasis from sending magnetic media such as tape to telephonic transmission of text processed on WYLBUR files.

We have been investigating the interaction of microprocessors with mainframe systems to learn how

best to distribute the successive steps of initial keying, correcting, encoding and typesetting. The expected advent of the IBM Personal Computer will, together with the PSL Micom and Osborne units, bring to three the number of small systems that can be coordinated with WYLBUR programs and used to send coded information. (Many more small systems can, of course, transmit material to WYLBUR for later processing.)

Our activities have attracted attention and brought inquiry from several publishing groups in this country and abroad. Publishers are understandably uncertain about computerization and curious about our experience. In collaboration with the Biophysical Society, we recently surveyed its members to learn that some 80 percent of the respondents can prepare papers on word processors and about 50 percent should have modern capability. These figures reveal the abundant source of "compuscripts" that can now be processed using the methods being developed here.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER	
NOTICE OF INTRAMURAL RESEARCH PROJECT		Z01 CT00041-05 PSL	
PERIOD COVERED			
October 1, 1982 to September 30, 1983			
TITLE OF PROJECT (50 characters or less. Title must fit on one line between the tildes)			
Quantitative Analysis of Cell Structure, Membranes and Organ Development			
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent page)			
(Name, title, laboratory, and Institute affiliation)			
N. Gershon, Ph.D., Visiting Scientist, PSL, DCRT			
COOPERATING UNITS (if any)			
K. Nassal, Ph.D., PSL, DCRT; K. Porter, Ph.D., Fogarty Scholar, Fogarty International Center and University of Colorado, Boulder, CO; B. Trus, Ph.D., CSL, DCRT; E. Martino, Ph.D., CSL, DCRT			
LABORATORY			
Physical Sciences Laboratory			
SECTION			
INSTITUTE AND LOCATION			
Division of Computer Research and Technology			
TOTAL MAN-YEARS	0.8	PROFESSIONAL	0.7
		OTHER	0.1

Quantitative Analysis of Cell Structure, Membranes and Organ Development

We have developed a new method for the three-dimensional reconstruction of cellular structure in order to understand this structure at a macromolecular level and how structure is related to biochemical and biological function. We use electron micrographs produced by a high voltage electron microscope (a national resource sponsored by NIH) in Boulder, Colorado and other electron and light micrographs taken at NIH. This method was extended to a microcomputer with high resolution color graphics.

Software for the image digitization, alignment-of-sections and for the whole image reconstruction from the separate sections has been accomplished. We continue now to develop software for realtime rotation and image representation in three- and two-dimensions.

This methodology will be employed to determine the organization of microtubule nucleation centers in cells. It will be important for studies of the determinants of cell shape and development. Cytoplasmic structure and diffusion within cells will be also analyzed. In addition, studies of embryonic and brain development are planned using this newly constructed facility.

The second part of this project is concerned with volume, surface area, and space for diffusion of the cytoplasmic matrix. We developed a new image analysis method to measure the volume fraction and the surface area occupied by cells by the gelatinous cytoplasmic matrix (the cytoskeleton and microtrabecular lattice). It involves analysis of electron microscopic data using a video frame buffer (DCRT's Evans & Sutherland System). The results obtained so far show that these structures occupy no more than 10-30 percent of the cytoplasmic volume. Comparing it with protein diffusion results yielded values for binding energies of proteins to the cytoplasmic matrix. A study on the effect of osmotic conditions on the volume of the cytoplasmic matrix has been initiated and will be further studied. The use of these techniques will be extended to study immunocytochemical systems.

Publications:

Gershon, N., Porter, K., and Trus, B.: The microtrabecular lattice and the cytoskeleton. Their volume, surface area and the diffusion of molecules through it. *Proceedings of the Katzir-Katchalsky Memorial Symposium* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00068-04 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Diffusion of Molecules on Cell Surfaces and Light Scattering from Fluids		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) N. Gershon, Ph.D., Visiting Scientist, PSL, DCRT		
COOPERATING UNITS (if any) B. Aizenbud, Ph.D., M.I.T., Cambridge, MA		
LAB/BRANCH Physical Sciences Laboratory		
SECTION		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MANYEARS 0.2	PROFESSIONAL 0.1	OTHER 0.1

Diffusion of Molecules on Cell Surfaces and Light Scattering from Fluids

Membranes are usually assumed to be planar when diffusion coefficients are calculated from the results of fluorescence photobleaching recovery (FPR) experiments. It was shown that for a model system, that under typical conditions of membrane topography, and for the particular geometry of spot FPR, the calculated diffusion coefficient can be weakly sensitive to the microvilli length. However, an anisotropic nonplanarity of membrane might lead to anisotropic diffusion that can be detected by pattern FPR. We found that surface corrugation alone cannot explain the reported value of diffusion anisotropy.

Publications:

- Aizenbud, B., and Gershon, N. D.: Diffusion of molecules on biological membranes of nonplanar form—a theoretical study. *Biophys. J.* 38: 287-293, 1982.
- Aizenbud, B., and Gershon, N. D.: Diffusion of molecules on microvillous biological membranes. In Perelson, A. C., DeLisi, C., and Wiegel, F. W. (Eds.): *Cell Surface Phenomena*. New York, Marcel Dekker (in press).
- Aizenbud, B., and Gershon, N. D.: Hydrodynamic equations and VH light scattering from viscoelastic (solid-like) systems. II. Molecular approach. *Physica* 108A: 583-588, 1981.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00108-01 PSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Effect of Solvent on Biological Macromolecules		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) B. Lee, Ph.D., Expert, PSL, DCRT		
COOPERATING UNITS (if any) V. A. Parsegian, Ph.D., PSL, DCRT; D. Rau, Ph.D., NIADOK		
LAB/BRANCH Physical Sciences Laboratory		
SECTION		
INSTITUTE AND LOCATION Division of Computer Research and Technology		
TOTAL MANYEARS 0.4	PROFESSIONAL 0.4	OTHER 0.0

Effect of Solvent on Biological Macromolecules

Solvent can interact with the biological macromolecules in two ways. It can bind to the solute strongly and specifically, giving rise to, among other things, the hydration force. With V. A. Parsegian and D. Rau, we measured the magnitude of this force between DNA double helices. This aspect of the study is reported by Parsegian. In addition, we compared the protein-protein interactions that occur in the crystal with those between the subunits in multimeric protein complexes. We found that the former is generally more complex than the latter but few other generalizations were possible. This aspect of the study will continue.

The solvent can also influence the behavior of macromolecules in a general and nonspecific way. Study of this aspect generally coincides with the study of the hydrophobic phenomenon. This was studied using statistical mechanical methods. I have succeeded, for example, in finding the physical origin of the hydrophobic volume shrinkage phenomenon and in computing the extent of volume fluctuation of globular protein molecules. However, in order to properly apply this rigorous procedure to biological macromolecules, a way must be found that will handle nonspherical solutes. A new approximation scheme was discovered to this end, and future efforts will be concentrated on developing this approximation scheme.

Publications:

- Lee, B.: Calculation of volume fluctuation for globular protein models. *Proc. Natl. Acad. Sci. USA* 80: 622-626, 1983.
- Lee, B.: Partial molar volume from the hard-sphere mixture model. *J. Phys. Chem.* 87: 112-118, 1983.

**COMPUTER-BASED STUDIES MATHEMATICAL THEORETICAL
PUTING SINGULAR VALUE DECOMPOSITION DATA
MATHEMATICS MEDICAL APPLICATIONS STATISTICS
RECOGNITION IMAGE PROCESSING BIOMEDICAL
ES PARTIAL DIFFERENTIAL EQUATIONS ADAPTIVE**

Laboratory of Applied Studies

John E. Fletcher, Acting Chief

Clinical Research and Patient Care

Computer-based studies of physiology and pathophysiology during exercise. R. Burgess, M. Horton, E. Pottala, J. Bailey (LAS); A. Nienhuis, R. Crystal (NHLBI). In this project, breath-by-breath analyses of pulmonary gas exchange performed by a laboratory minicomputer-based system are the bases for studies of oxygen delivery to tissue in normal states and in pulmonary, cardiovascular, and hematologic pathophysiologies. Serial testing of a patient provides objective indications of severity of disease and efficacy of treatment. A protocol for studying drug therapy in patients with sickle cell disease is being carried out.

Computer-based method of monitoring central nervous system function in critically ill patients. R. Burgess, M. Horton, E. Pottala, J. Bailey (LAS); C. Natanson, J. Parrillo (CC). The goal of this project is to develop a microcomputer-based system for analysis and display of scalp-recorded neuroelectrophysiological signals following programmed stimuli (i.e., evoked potentials). These stimuli will permit one to estimate and to follow CNS (especially cerebral) function in critically ill patients. Most of the equipment that was designed in the previous year for the system has been procured; hardware interfacing and basic software development have been initiated.

Computer systems for nuclear medicine. M. Douglas, J. Bailey, R. Burgess (LAS); S. Bacharach, et al., (CC, Nuclear Medicine); R. Bonow (NHLBI). This project involves development and application of computer methods to such diagnostic imaging activities as ECG-gated radionuclide ventriculography and dynamic scintigraphic studies of other organs (e.g., kidneys, lungs). Extensive studies of regional time-activity curves in radionuclide ventriculography have revealed important relationships between the harmonic content of the curves, their signal-to-noise ratios, and their average scintillation counts. This relationship determines the reliability of various parameters of regional cardiac function as well as the optimum design for filtering the curves. A study of gallium scans has revealed that the routine, noncomputerized scans have a very narrow window for intensity response and hence

the clinicians are not seeing all the information potentially available through computer processing.

Computer analysis of electrocardiograms. J. Bailey, M. Horton (LAS); D. Savage, S. Palmeri (NHLBI); L. Jackson (Georgetown University Medical Center). The continuing goals of this project have been to evaluate the diagnostic power and epidemiological utility of the leading computer programs for ECG interpretation. ECG data on several thousand cases from the Framingham study have been collected. Of these, five to six percent also have echocardiographic evidence for left ventricular hypertrophy. The most accurate ECG indicators of this condition are being identified in these data. The ECG Laboratory of Georgetown University Medical Center has collected simultaneous 12-lead data on well-documented, normal and abnormal cardiac patients; this data base also is being examined to compare diagnostic accuracy of the Hewlett-Packard, the IBM, and the Marquette ECG programs in a collaborative study with LAS and NHLBI.

Statistical research in clinical pathology. E. Harris, M. Horton, A. Albert (LAS); G. Shakari, D. VanSant (DMB); clinical chemists and others in the U.S.A., Europe, and Japan. This research involves application of statistical theory to clinical laboratory tests, including serial studies of blood chemistries in health and disease. A collaborative study to explore relative sensitivities of subject-specific, univariate and multivariate decision criteria has progressed through identification and collation of data from approximately 100 outpatients with independently diagnosed liver dysfunctions. A previously reported method for deriving reference differences as criteria to evaluate observed changes has been extended to trends, and effects of analytic variation on the sensitivity of these criteria have been determined. In collaboration with clinical pathologists, this method is now being applied to selected categories of inpatients.

Laboratory Investigations

Computer analysis of electron and x-ray micrographs. M. Douglas, J. Bailey (LAS); J. Costa (NIMH). This project involves the development and

implementation of mathematical models and image enhancement techniques to analyze computer-acquired information from electron energy-loss and x-ray spectra indicating the location of extremely small quantities of important chemical elements and active protein molecules within cells. Dense bodies in electron micrographs of blood platelets are being examined currently with this system.

Hybrid computing to analyze physiologic signals. E. Pottala, H. Le, J. Bailey (LAS); J. Dvorak (NIAID); M. Postan (WHO); W. van Arsdel (FDA). This project uses the LAS minicomputer system (MAC-16) for analysis of biological signals (ECG, EMG, EEG, etc.). This year, methods for acquiring and analyzing rodent electrocardiograms were developed so that animal models of drug-induced cardiotoxicity (FDA) and myocardial infections (NIAID, WHO) could be studied.

Mathematical modeling of biological processes. J. Fletcher (LAS); R. Schubert (Louisiana Tech. Univ.). Mathematical models that describe the relationships between free and facilitated substrate diffusion, metabolism, and microcirculatory flow transport are being developed and evaluated. These models can identify the critical physiological parameters for substrate supply to tissue and to their ranges in normal and pathophysiological states. Exploration of a new unified model for perfused organ experiments has continued. Limits of capillary wall permeabilities were developed, and some analysis of the effects of Michaelis-Menten kinetics is underway. A reexamination of model conditions when hemoglobin and/or red cells are present in the perfusing fluid is also in its early stages.

Network modeling in biology. B. Bunow, E. Pottala (LAS); T. Colburn (NIMH); and other NIH, FDA, and NIOSH scientists. LAS has shown that network simulation languages (e.g., NET2, SPICE), operating on NIH central computers and VAX systems at NIMH, NCI, and NIADDK, provide a powerful modeling tool for NIH scientists who are modeling neural, electromechanical, and biochemical systems.

Active transport, biochemical kinetics, and their interactions. B. Bunow (LAS); D. Mikulecky (Medical College of Virginia); J. Kernevez (Univ. of Tech.,

Compiègne, France); R. Hendler (NHLBI). This project examines experimental and mathematical studies of kinetics and thermodynamics of biological processes involving enzyme-catalyzed reactions. Thermodynamic principles and mathematical analysis were applied, in collaboration with NIH scientists, to problems in membrane transport, bioenergetics, and ligand binding. A kinetic description of simultaneous reaction and transport has been developed that shows the inadequacy of previous irreversible thermodynamic approaches.

Computer Research and Software Development

Mathematical and computational methods for solving nonlinear equations. R. Shrager (LAS); R. Hendler, R. Kincaid (NHLBI); B. Kamgar-Parsi (University of Maryland). A root-finder for one equation in one unknown has been developed that converges to a local root and determines machine precision of that root. The method converges in reasonable time despite poor initial estimates. A minimizer of a function of several variables has been coded, and is being extended to handle linear constraints. Algebraic-differential systems that contain both nonlinear algebraic and differential equations have considerable application in biochemistry and pharmacokinetics. Software to solve these systems is being designed and investigated. The rootfinder, the minimizer, and the algebraic-differential systems solver are all intended for eventual inclusion in MLAB. Immediate research applications of this project include simulation of whole blood oxygen saturation, calmodulin-calcium-magnesium interactions, oxygen uptake by mitochondria, and GABA metabolism as affected by hepatic failure in rabbits.

Numerical methods for the solution of mathematical models describing reaction-diffusion and other processes in biological systems. M. Bieterman, J.E. Fletcher (LAS); I. Babuska (University of Maryland). This project is concerned with the investigation, development, and implementation of numerical solution methods for systems of partial differential equations that are used to model dynamic

physiological processes. Adaptive finite element methods have been applied to and are shown to be effective for models of facilitated diffusion in tissue, population ecology and genetics, hyperthermia studies involving models of bioheat transfer, and models for nerve conduction. Software packages implementing these methods are now available on the IBM System 370 and on the DECsystem-10.

Research Projects

DEPARTMENT OF HEALTH AND HUMAN SERVICES: PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00034-07 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the brackets) Computer-based Studies of Physiology and Pathophysiology During Exercise		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) R.C. Burgess Senior Staff Fellow LAS DORT		
COOPERATING UNITS (if any) M.R. Horton Computer System Analyst, LAS DORT CHB, NHLBI: PB, NHLBI: LCB, NIAIDDK		
LAB BRANCH Laboratory of Applied Studies		
SECTION Medical Applications Section		
INSTITUTE AND LOCATION NIH, DORT, Bethesda, MD 20205		
TOTAL MAN-YEARS 1.65	PROFESSIONAL 1.50	OTHER 0.15

Computer-based Studies of Physiology and Pathophysiology During Exercise

This project, through a collaborative effort of LAS with the Clinical Hematology and Pulmonary Branches of NHLBI, is directed toward a deeper understanding of the physiology and pathophysiology of oxygen transport to tissues through the use of computerized breath-by-breath analysis of gas exchange and computer-based models of ventilation and oxygen transport.

Progress in FY83: The hardware obtained during FY81-82 has been configured into a comprehensive computerized exercise laboratory. Software developments include:

1. automatic control of the time-dependent exercise regimen on the bicycle ergometer or treadmill, according to a design customized to each patient;
2. facilitated daily calibration of sensors, through extensive operator prompting;

3. acquisition of multichannel data in realtime, conversion to actual units, and correction for humidity and barometric pressure;
4. processing of data online to derive breath-by-breath parameters of gas exchange; and
5. entry of patient/study identification information to be stored with the computed breath-by-breath parameters.

A study to evaluate the use of several classes of vasodilators in sickle cell anemia has been underway since October 1982. Testing of Hydralazine has been concluded. The side effects of Hydralazine (primarily tachycardia, fever, and rash) precluded the demonstration of any beneficial effect. However, the exercise laboratory has proved its capabilities as an effective and objective tool for evaluating morbidity and therapeutic efficacy in sickle cell disease.

Proposed Course: Further refinement of the software to improve detection of the anaerobic threshold and other functional measures has begun. A significant focus of the FY84 effort will be the development of clinically usable displays of both realtime data and computed parameters.

Large scale testing of normal volunteers will be carried out and correlated with other measures of fitness. A preliminary test of Nifedipine in sickle cell disease suggests that it may be beneficial; an expanded study of this agent will be pursued during the coming year. An experimental protocol to evaluate the effect of colchicine in patients with sarcoidosis has been submitted in collaboration with the Pulmonary Branch, NHLBI, to the Human Experimentation Committee for approval.

DEPARTMENT OF HEALTH AND HUMAN SERVICES-PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00098-02 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (If characters or less. This must fit on one line between the borders.) Computer Based Method of Monitoring the CNS in Critically Ill Patients		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) R.C. Burgess Senior Staff Fellow LAS DCRT		
COOPERATING UNITS (if any) Critical Care Medicine, Clinical Center		
LAB/BRANCH Laboratory of Applied Studies		
SECTION Medical Applications Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL YEARS 1.05	PROFESSIONAL 0.90	OTHER 0.15

Computer Based Method of Monitoring the CNS in Critically Ill Patients

This project is a joint effort between the Laboratory of Applied Studies and the Department of Critical Care Medicine to design, build, and implement a highly clinically oriented, distributed-processing, microcomputer-based system for analysis and display of scalp-recorded neuroelectric signals.

This tool will be used to investigate the degree of dysfunction in neurologically impaired patients, correlate the indices developed with other measures of cerebral function, and evaluate the effectiveness of various therapeutic interventions.

Background and Objectives: In the critically ill patient with multiple organ dysfunction, impaired brain function frequently coincides with deterioration of other major systems. However, the degree of damage and capacity for restoration of the brain does not necessarily parallel that of the rest of the body. In addition, assessment of the central nervous system is hampered by limitations imposed by procedures (e.g., endotracheal intubation) and/or drugs (e.g., Pavulon).

The initial phase of this project is directed toward the development of a comprehensive, mobile, neurodiagnostic system including:

1. a precision analog front end for low-noise detection, amplification, and filtering of the spontaneous and evoked EEG activity;

2. devices to deliver programmed, visual, auditory and somatosensory stimuli;
3. a central processor with intelligent peripherals for data acquisition, manipulation, calculation, and storage; and
4. a display capable of high resolution graphics and printout for presentation of current and past data, trends, and interpretive imaging.

After initial development and testing has been completed, the system will be used in the Critical Care Unit, Clinical Center, to address the following questions:

- Which electrophysiological parameters can be used to best follow the functional neurologic status of the patients?
- What is the optimal protocol for obtaining data in order to balance recording requirements and nursing care needs?
- How can the parameters be best combined into a meaningful profile and be best displayed to provide comprehensive, yet easy-to-assimilate, clinical information?
- How does the information offered by this system compare to other neurodiagnostic techniques?
- How does this system improve care of the patient and understanding of the pathophysiologic dynamics?

Progress in FY83: The equipment specified in the system design that was accomplished in FY82 has been procured. Custom mechanical and electronic fabrication is underway. Equipment has been mounted in a specialized rack that can be wheeled to the bedside of the patient to be monitored. Design of the interface between the host CPU and the array processor has been completed. The design of software to control simultaneous stimulation, data acquisition, storage, and display in the realtime environment has been initiated.

Proposed Course: Extensive development of both hardware and software will be carried out during the coming year. Acquisition of noise-free, microvolt-level signals from the patient's scalp in the electrically hostile environment of the Critical Care Unit is crucial to reliable semi-automatic monitoring of CNS function. To accomplish this task a computer controlled, IEEE-488

compatible, front-end preamplifier/filter will be completed. Multiple algorithms for extracting functional information from multimodal evoked potentials will be implemented.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00003-12 LAS
PERIOD COVERED October 1, 1983 to September 30, 1983		
TITLE OF PROJECT (50 characters or less. Title must fit on one line between the borders.) Computer Systems for Nuclear Medicine		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages (Name, title, laboratory, and institute affiliation) M.A. Douglas Computer System Analyst LAS, DCRT		
COOPERATING UNITS (if any) R.C. Burgess Senior Staff Fellow LAS, DCRT Nuclear Medicine, Clinical Center; CB, NHLBI		
LAB BRANCH Laboratory of Applied Studies		
SECTION Medical Applications Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MAN-YEARS 0.95	PROFESSIONAL 0.80	OTHER 0.15

Computer Systems for Nuclear Medicine

This project involves computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Nuclear Medicine Department of the Clinical Center and collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiology and myocardial perfusion scintigraphy, renal dynamics, and pulmonary ventilation-perfusion relationships.

Progress in FY83: Cardiac Scintigraphy: In collaboration with Nuclear Medicine and the Cardiology Branch, LAS has investigated more than 40 parameters related to mobility of the heart wall. These parameters include ejection fraction, regional emptying time, relative emptying time, relative stroke volume, phase (of the first Fourier harmonic), and maximum ejection rate. All parameters were generated for all cases in a data base consisting of 40 normal volunteers, 24 patients with coronary disease and known resting apical abnormalities (akinesis or dyskinesis), and 15 patients with cardiomyopathy. The power of each parameter to discriminate between these 3 groups has been evaluated. Global ejection rate and global filling fraction are the parameters that discriminate best between normal and abnormal cases. Relative stroke volume and regional ejection time in the apical regions are the best separators of apically normal from apically

abnormal cases. A manuscript describing this study is being prepared.

Investigation of the signal to noise and Fourier harmonic content of global and regional time activity curves (TAC's) has been completed. This study showed that the physiological signal is largely described by four or fewer harmonics and that regions smaller than one-fourth of the ventricular region of interest produce TAC's that cannot be distinguished from background in terms of S/N ratio or harmonic content.

In conjunction with the Institute for Nuclear Medicine, University of Utrecht, the Netherlands, algorithms for the automatic localization of structure in cardiac scintigraphy have been refined and tested on data from 867 cases. Also, methods of detection of regions of abnormal ventricular contraction have been investigated.

A model has been developed to demonstrate the effect of noise on the reliability of the various parameters characterizing the TAC's. Tables for parameters of interest, such as ejection time and time to end systole, have been prepared. Each parameter's table gives several S/N ratios and the associated error in the computation of the parameter. This sensitivity analysis provides an indication of the accuracy of the parameters in clinical use where some background noise is unavoidable.

Whole body Gallium images are being investigated by computer methods. The goal of this project is to improve the quality and repeatability of the Gallium Index for lungs, which correlates with active inflammation. Preliminary data has been acquired and analyzed at a resolution of 128 x 128 picture elements for the whole body. Lungs are outlined, and their isotope uptake is expressed as a percentage of total body uptake. Early results indicate that noncomputerized scans have a very narrow intensity window and hence the clinicians are not seeing all the information potentially available through computer processing.

Renal Scintigraphy: Further documentation of changes in dog kidneys after ligation of a segmental renal artery was obtained by gross and histologic necropsy

examination. Visualization by functional mapping techniques, which had been redeveloped in FY80-82, correlated well with contrast angiography and necropsy findings. However, an important necropsy finding was that the lesions induced by segmental artery ligation tended to be distributed in a coronal plane on the dorsal or ventral surface, which was parallel to the plane of the crystal in the scintigraphic camera. Therefore, the focal nature of the lesion could not be demonstrated in the scintigraphic data. The model was redesigned with a clearer focal lesion to test further the diagnostic potential of the functional image technique; however, this project had to be deferred because the new medical staff fellow who was to continue this work, was unable to accept an NIH appointment as agreed during FY82 recruitment.

Pulmonary Scintigraphy: Further work in ventilation/perfusion scintigraphy has been deferred until the appropriate personnel can be recruited.

Proposed Course: Cardiac Scintigraphy: A statistical analysis of the existing data base will be continued. A possible outcome of this might be a discriminant function using various parameters to achieve an optimal separation of normals from abnormals. Efforts will be made to expand the data base in order to obtain better statistical reliability. Another interesting study will involve those patients with myopathy secondary to adriamycin therapy, using each patient before therapy as his own control. Other patients who have normal contractility at rest but abnormalities upon exercise form an additional interesting data base.

The new disk system of the DeAnza display terminal is now operational. This should facilitate study of paired myocardial (Thallium) and blood pool image sequences. Refined end-diastolic and end-systolic edge detection, methods of left ventricle segmentation, assessment of wall motion abnormalities and perfusion, and more accurate determination of volumes are planned.

The Gallium study will begin to acquire and analyze images at an increased resolution of 128 x 256 or 128 x 512 picture elements. A calibrated radionuclide source is to be placed in the field of view in order to allow quantification of the uptake. An index of the homogeneity of uptake (or lung texture) is to be

developed and tested. Automated lung boundary definition is to be studied.

Publications and Abstracts:

- Bacharach, S.L., Green, M.V., Vitale, D., Douglas, M.A., White, G., Bonow, R.O., and Jones, A.E.: A minimum error method for temporal fourier filtering of gated cardiac data. Eighth Conference on Information Processing in Medical Imaging (in press).
- Bacharach, S.L., Green, M.V., Vitale, D., White, G., Douglas, M.A., Bonow, R.O., and Jones A.E.: Optimum number of harmonics for filtering Cardiac Volume Curves. *J. Nucl. Med.* 24:17, 1982.
- de Graaf, C.N., Douglas, M.A., Findley, S.M., van Rijk, P.P., Bacharach, S.L., Green, M.V., and Bonow, R.O.: Een algoritme voor het localiseren van structuren in scintigrafische beelden. *Nucleair Geneeskundig Bulletin* 4:42-48, 1982.
- Douglas, M.A., Bailey, J.J., van Rijk, P.P., Bacharach, S.L., Bonow, R.O., and Green, M.V.: Analysis of regional function in radionuclide ventriculography: Physiological signal, scintillation noise, and regional size. *Computers in Cardiology*. Silver Spring, MD, IEEE Computer Society, 1983, pp. 315-318.
- van Rijk, P.P., Bailey, J.J., and de Graaf, C.N.: Gecomputeriseerde methoden voor de detectie van regionale ventriculaire contractieabnormaliteiten. *Nucleair Geneeskundig Bulletin* 4:49-54, 1982.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00002-13 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983.		
TITLE OF PROJECT (40 characters or less. This must fit on one line between the borders.) Computer-Aided Analysis of Electrocardiograms		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) J.J. Bailey Chief, MAS, LAS, DCRT		
COOPERATING UNITS (if any) M.R. Horton Computer System Analyst, LAS DCRT ECG Lab, Clinical Center ECG Lab, Georgetown Medical Center		
LABORATORY Laboratory of Applied Studies		
SECTION Medical Applications Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL WANTED:	PROFESSIONAL	OTHER
0.55	0.40	0.15

Computer-Aided Analysis of Electrocardiograms

These studies, continuing since 1970, are directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer programs for analysis of resting electrocardiograms (ECG's). Further studies will involve new methods of feature extraction and design of criteria by computer techniques and their use in epidemiological studies.

Data on several thousand cases from the Framingham study have been collected. About five to six percent of these cases also show evidence of left ventricular enlargement by two-dimensional echocardiography. In the younger population slight enlargement is associated

with a vigorous athletic lifestyle and an absence of ECG stigmata for LVH. In the older population, LVH tends to be more concentric, more pronounced, and more often associated with other problems (e.g., hypertension) and with positive ECG evidence of LVH. The variety of cases in this data base allows extensive testing of ECG algorithms for LVH.

The vendor for the Hewlett-Packard ECG system in the ECG Laboratory of the Clinical Center finally has supplied programs and information so that the system can accept digitized ECG's from outside sources. With this extended capability, work involving a test of three ECG programs (IBM, H-P, and Marquette) utilizing simultaneous 12-lead ECG data, generated at Georgetown University Medical Center on patients with non-ECG documentation of their disease, is proceeding apace.

Proposed Course: Further detailed analysis of the Framingham ECG data and correlations with non-ECG data are planned.

The ECG Laboratory at Duke University Medical Center has proposed joining the Georgetown-NIH ECG study. The Duke Program will add a fourth ECG evaluation program to the study.

The Laboratory of Systems and Bioengineering (LADSEB), National Research Council of Italy, is investigating the use of fuzzy set theory to assign a degree of membership to a diagnostic category. Degree of membership lends stability to the diagnostic statement, in contrast to the classical, discrete, threshold/decision tree method now used by most ECG programs. On the other hand, this approach is not constrained to treat diagnostic categories as disjoint sets as is the multivariate statistical (multi-Bayesian) approach of Pipberger and Cornfield. LAS will provide data and consultation in collaboration with the LADSEB.

Publications and Abstracts:

Bailey, J.J., Berson, A.S., Jackson, L.K., Stevens, J.M., Tolan, G.D., and Wolf, H.K.: Evaluation methodologies for ECG diagnostic systems. In Bonner, R.E., Pryor, T.A., Laks, M.M., and Cole, S.S. (Eds.): *Computerized Interpretation of the Electrocardiogram VI*. New York, Engineering Foundation, 1981, pp. 53-62.

Macfarlane, P.W., Chen, C.Y., and Bailey, J.J.: A comparison of point scoring techniques for the diagnosis of LVH. In de Padua, F., and Macfarlane, P.W., (Eds.): *New Frontiers in Electrocardiology*. Wiley, 1981, pp. 353-356.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		701-170000-15 LAS
PERIOD COVERED		
October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (See chapters on page 2) This must fit on one line between the borders.		
Statistical Research in Clinical Pathology		
PRINCIPAL INVESTIGATOR (List of her professional personnel on following pages)		
Name, title, laboratory, and multiple affiliation:		
E.A. Harris		
COOPERATING UNITS (if any)		
LAB BRANCH		
Laboratory of Applied Studies		
SECTION		
INSTITUTE AND LOCATION		
ICP, NIH, Bethesda, MD 20205		
TOTAL MANTLE	PROFESSIONAL	OTHER
0.45	0.50	0.15

Statistical Research in Clinical Pathology

Univariate and multivariate time series models and discriminant techniques are being applied to various data bases consisting of short series of measurements of serum biochemistries in healthy subjects and patients with myocardial infarction. The purpose is to gain practical experience in the use of these statistical, predictive techniques to detect changes and trends within individuals, taking into account biological variation and measurement error. The time scale of these series varies from daily to weekly, 6-month, and 12-month intervals between observations. Parallel computer-based simulation studies are also underway, particularly to estimate the relative sensitivities and specificities of multivariate and univariate forecasting methods. Mathematical investigations into the properties of a new stochastic model of linear change are continuing.

Objectives: To investigate applications of statistical theory, particularly the use of variance components, discriminant analysis, and the theory of discrete and continuous time series, to the interpretation of serial clinical laboratory measurements in healthy subjects and patients with acute and chronic disease.

Progress in FY83: The development of a statistical method for estimating "reference change" (critical differences between successive measurements of a

biochemical constituent in an individual) has been completed. Initial application has been to serial observations of calcium and alkaline phosphatase in healthy subjects. A paper describing the method and its uses has been published. Collaborative studies applying this method to patients with acute and chronic diseases have begun at NIH and at the University of Virginia with the aid of a comprehensive computer program operating under the powerful statistical system, SAS.

Study of the sensitivity of multivariate reference regions based on subject-specific data has progressed continuously but slowly during the year. A group of patients with specified liver dysfunctions during the years 1974 to date has been identified from the medical records of the Perfect Liberty Health maintenance program in Osaka and Tokyo. The specific variables for inclusion in the serial multivariate vector of each patient remain to be defined.

Statistical methodology for evaluating the effects of analytic error on the detection of trends in biochemical measurements has been formulated and simulation studies have been completed. These methods are based on simple autoregressive models of serial change. The effects of improvements in analytic precision have been assessed, using currently recommended limits of analytic error as guidelines. The results are described in a manuscript to be published.

Dr. A. Albert's Fogarty International Research fellowship terminated in August, 1982, and he has returned to the University of Liege, Belgium. However, during FY83, he completed and published his major work while in LAS, a theory of discriminant analysis adapted to serial multivariate vectors (multivariate response curves). He has used this theory to derive sequential risk probabilities of outcome following myocardial infarction and diseases of children admitted to intensive care. Papers on both these areas of application have been either published or submitted for publication.

Proposed Course: During this reporting year, the principal investigator retired from government service but was extended "guest worker" status until September 30, 1983. This project is therefore terminating as an LAS-supported activity. However,

investigators in the collaborating NIH laboratories may seek to continue the intramural studies.

Publications and Abstracts:

- Albert, A.: Discriminant analysis based on multivariate response curves: a descriptive approach to dynamic allocation. *Statistics in Medicine* 2:95-106, 1983.
- Albert, A., Chapelle, J.P., Heugshem, C., Kulbertus, H.E., and Harris, E.K.: Evaluation of risk using serial laboratory data in acute myocardial infarction. In Heugshem, C., Albert, A., and Benson, E.S. (Eds.): *Advanced Interpretation of Clinical Laboratory Data*. New York, Marcel Dekker, 1982, pp. 117-130.
- Albert, A., and Ruttimann, U.: Prediction of an ordered categorical response variable from serial measurement. *Biometrics* (in press).
- Harris, E.K.: Addendum to recent paper on reference values for change. *Clinical Chemistry* (in press).
- Harris, E.K.: Regression, least squares, and correlation. In Seligson, D., M.D. (Ed.): *Handbook of Clinical Chemistry* (in press).
- Harris, E.K.: The effects of reductions in analytic variance on the early detection of trends. *Proceedings of the Fourth International Meeting on Clinical Laboratory Organization and Management* (in press).
- Harris, E.K., and Yasaka, T.: On the calculation of a "reference change" for comparing two consecutive measurements. *Clinical Chemistry* 29:25-30, 1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER
		Z01 CT00042-05 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (If 40 characters or less, title must fit on one line; otherwise the title may be truncated to fit on one line.) Image Processing in Electron Microscopy and X-ray and Electron-loss Spectroscopy		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institution affiliation) M.A. Douglas Computer Systems Analyst LAS DORT		
COOPERATING UNITS (if any) Clinical Neuropathology Branch, NIMH		
LAB/BRANCH Laboratory of Applied Studies		
SECTION Medical Applications Section		
INSTITUTE AND LOCATION DART, NIH, Bethesda, MD 20205		
TOTAL HOURS: 0.85	PROFESSIONAL: 0.70	OTHER: 0.15

Computer based analysis and image processing in electron microscopy and x-ray and electron-loss spectroscopy

This project is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally x-ray micrography and electron energy loss spectra derived from the electron microscopy image of biological specimens.

Progress in FY83: Hardware problems in the DeAnza image processing system have been corrected by the

vendor. Incompatibilities between the DeAnza system and the magnetic tape and disk peripherals are in the process of being resolved. The disk drive is currently operational at a submaximal performance level. A series of 512 x 512 pixel electron micrographs of dense bodies in human platelets before and after the addition of fluorine have been acquired at the electron microscope facility of Brookhaven National Laboratories. These micrographs have been analyzed and the dense bodies detected and delineated by two different operators, each using a semi-automated edge detection algorithm. Densities of each detected dense body have been computed. Statistical analyses are being performed on the data to determine the sample size necessary to detect reliably the changes in density of dense bodies in digitally-acquired, electron micrographs of platelets.

Proposed Course: When the communications problems between the DeAnza system and its peripheral devices have been resolved, important work with phantoms and specimens of known composition then may commence. This work is necessary in order to formulate appropriate mathematical/statistical models to investigate changes in the composition of platelets. At that time the signal to noise ratio in phantoms and biological specimens also will be examined. The effect of contamination and specimen destruction by the high energy electron beam will be investigated. Efforts will continue in the development of algorithms for image enhancement and for automated element recognition and delineation.

Investigation of Hybrid Computing for the Analysis of Physiologic Signals

This project uses hybrid computing techniques to analyze physiologic signals such as electrocardiograms, electroencephalograms, and electromyograms.

Progress in FY83: Over 200 ECG's from rats on various nutritional or drug protocols have been collected by pharmacologists at FDA. The methods of A/D conversion, filtering, baseline corrections, beat averaging, and vector loop generation have been developed and debugged.

Proposed Course: Investigators at NIAID have experimentally infected mice with Trypanosomi Cruzi and thereby developed an animal model of Chagas' disease. The computer methods for analyzing rat ECG's will be applied to the ECG's being collected from these mice.

Review of both rat and mouse ECG's will be necessary to determine which feature parameters will be the most accurate indicators at pathology. The design of feature extraction and parameter measurement will require a new analytical effort, because rodent ECG's differ considerably from human ECG's in many features, including a much higher frequency content.

The MAC-16 system will have continued use for ECG processing for the Framingham Heart Study (see project report on electrocardiography), as well as for processing the rodent ECG's.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00004-12 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Investigation of Hybrid Computing for the Analysis of Physiologic Signals		
PRINCIPAL INVESTIGATOR (Last other professional personnel on exchange) (page) Name: E.W. Pottala, Electrical Engineer, LAS DCR		
COOPERATING UNITS (if any) Laboratory of Parasitic Disease, NIAID Division of Cardio-Renal Drug Products, FDA		
LAB BRANCH Laboratory of Applied Studies		
SECTION Medical Applications Section		
INSTITUTE AND LOCATION ICRI, NIH, Bethesda, MD 20205		
TOTAL MANYEARS 1.15	PROFESSIONAL 1.00	OTHER 0.15

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00005-13 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Mathematical Models of Binding Equilibria		
PRINCIPAL INVESTIGATOR (Last other professional personnel on exchange) (page) Name: J.E. Fletcher, Chief, Applied Mathematics Section, LAS DCR		
COOPERATING UNITS (if any) National Cancer Institute, Division of Cancer Treatment		
LAB BRANCH Laboratory of Applied Studies		
SECTION Applied Mathematics Section		
INSTITUTE AND LOCATION ICRI, NIH, Bethesda, MD 20205		
TOTAL MANYEARS 0.15	PROFESSIONAL 0.10	OTHER 0.05

Mathematical Models of Binding Equilibria

The objective of this project is the study of mathematical models of ligand-receptor or ligand-macromolecule binding studies at equilibrium.

The models are examined for mathematical as well as for conceptual validity and the models are explored parametrically to determine their suitability for fitting to experimentally obtained laboratory data. The appropriateness of various model fitting criteria are studied and general guidelines and computational algorithms are designed for computer-aided interactive model fitting.

Progress in FY83: No new analytical models were examined in FY83, although a number of literature critiques were requested by scientific journals, and an expository letter to the editor was published by *Mathematical Biosciences*.

Requests for copies of exportable computer algorithms continued to be filled and a number of brief Institute consultations were provided. A summary report including collected results from fifteen years of research in this area is being distributed.

The principal investigator continues to serve as a consultant, lecturer, and literature reviewer in this area.

Proposed Course: Consultations on new methodology and data analysis will continue to be made as they are requested by collaborating laboratories. Analytical development of new models and continued research in fitting methodology in this area will emphasize validation of experimental techniques, multi-receptor models, multi-ligand systems, and other special systems as required by collaborating investigators.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00044-05 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Mathematical Modeling of Substrate Transport in Physiological Environments		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) J.E. Fletcher Chief, Applied Mathematics Section LAS DCRT		
COOPERATING UNITS (If any) Dept. of Biomed. Engineering, LSU; Medical School, Univ. of Virginia		
LAB/BRANCH Laboratory of Applied Studies		
SECTION Applied Mathematics Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MAN-YEARS 0.65	PROFESSIONAL: 0.55	OTHER 0.10

Mathematical Modeling of Substrate Transport in Physiological Environments

Mathematical models of microcirculatory structure and function are developed from conceptual models into systems of coupled ordinary and/or partial differential equations. Methods of solution of these nonclassical formulations are developed and tested, and satisfactory cost effective methods are used to explore the properties of these models. The model simulations are interpreted in terms of microcirculatory physiology.

One objective of this project is to study whole organ response and organ tissue level phenomena by means of mathematical models in an effort to determine relationships between variables that govern the organ response to physiologic challenges.

Progress in FY83: Investigations continued into the modeling and analysis of red cell-free perfused organ experiments. A new model was examined for better compatibility with the experimental design. This model included capillary diffusion effects and examined the effects of a varying capillary wall permeability. One manuscript describing this model is in press, and two others have been submitted for publication. A fully satisfactory explanation of the tissue PO₂ histograms derived from these experiments has not yet been achieved.

Some additional investigations of models of red cell oxygen unloading have been carried out and the results indicate a very rapid release time. The question of

resistance to oxygen transport from intra-red cell oxyhemoglobin to cell mitochondria appears to require considerable reexamination. Previous explanations and quantitations appear to be in considerable error.

Research into both of the above areas will continue in FY84, but at a reduced level because of laboratory management demands on the principal investigator's time.

Publications and Abstracts:

Fletcher, J.E., and Schubert, R.W.: Capillary wall permeability effects in capillary-tissue structures. *Proceedings of 1983 ISOTT conference* (in press).
Fletcher, J.E., and Schubert, R.W.: Diffusional coupling in a hemoglobin-free perfused capillary-tissue structure. *Proceedings of the 1982 ISOTT meeting* (in press).

Fletcher, J.E., and Schubert, R.W.: On the computation of substrate levels in perfused tissues. *Mathematical Biosciences* 62:75-106, 1982.

Fletcher, J.E., and Schubert, R.W.: The theoretical prediction of substrate levels and their histograms in cell free perfused tissues. *Proceedings of the Oxygen Transport to Tissue-IV* (in press).

Schubert, R.W., Fletcher, J.E., and Reneau, D.D.: An analytical model for axial diffusion in the Krogh cylinder. *Proceedings of the 1983 ISOTT conference* (in press).

Schubert, R.W., Fletcher, J.E., and Reneau, D.D.: A simplified model for predicting myocardial PO₂ histograms. *Proceedings of the First Southern Biomedical Engineering Conference* (in press).

Simulation, computer programming, and formal language processing are the main tools in these investigations.

- Network Modeling in Biology with Existing Network Languages

Background and Objectives: Mathematical modeling in biology is especially difficult because of the need to be familiar with both the biological basis of the problems and the mathematical tools required for their solution. Network modeling, supplemented with effective languages for describing the models on computers, largely obviates the need for extensive mathematical sophistication, and makes the process of model formation and testing accessible to biologists lacking such skills. Topological modeling is particularly appropriate to biological problems because the objects of study generally satisfy conservation laws. In biological systems, the processes of flow, accumulation, and chemical transformation are fundamental; these are likewise the basic operations in network modeling.

Significance for Biomedical Research: The choice of a model for a biological process strongly conditions the design of experiments to confirm and test it. By making the analysis of models sufficiently simple and flexible, we intend to permit an investigator to consider many alternative models. From comparisons among the models using simulation, it should be possible to develop scientifically valid, rather than arbitrary, selection among the models. The network languages permit users to model phenomena that are too complex to be conveniently described and simulated in MLAB.

Progress in FY83: Progress in FY83 has been slowed by discovery of major incompatibilities between the NIH computer system and the computer system on which the NET-2 language was developed. Nevertheless, some software modifications have permitted the design of a retinal model and a model for a respirator.

A presentation on the ease and satelity of network modeling in biology was made to the Electrical Engineering department, University of Maryland. A workshop/tutorial in network modeling using NET-2 was given at Naval Surface Weapons Center.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00112-01 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (Do not exceed 100 characters; title must fit on one line between the borders)		
Network Modeling in Biology		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages)		
(Name, title, laboratory, and institute affiliation)		
B. Bunow Expert LAS DORT		
COOPERATING UNITS (if any)		
E.W. Portals	Engineer	LAS DORT
Medical College of Virginia; NIOSH, Blacksburg, Va.; LMB/NIAID; LSU/DORT		
LAS BRANCH		
Laboratory of Applied Studies		
SECTION		
Medical Applications Section		
INSTITUTE AND LOCATION		
DORT, NIH, Bethesda, MD 20205		
TOTAL MANYEARS	PROFESSIONAL	OTHER
0.55	0.40	0.15

Network Modeling in Biology

This project has two parts:

1. evaluation, comparison, and demonstration of the usefulness of network modeling languages for the description and simulation of complex biological models, and
2. the design, implementation, and documentation of a new network modeling language.

A model of subthreshold propagation of neural electrical signals, developed by W. Rall, NIADDK, was implemented in SPICE2. Numerical tables of signal amplitude at various points on the neuron, which were of higher accuracy than previously available, were constructed for neuroscientists studying these phenomena on actual neurons in the laboratory.

Future Course: Several NIH laboratories at NICHD and NIADDK now use network modeling extensively and this project will continue to provide consulting assistance. NET-2 will be modified to restore full IBM System 370 compatibility. A course in elementary NET-2 programming will be offered again in DCRT. This course is anticipated to bring new groups of users and collaborators.

- A New Network Modeling Language

Background and Objectives: The weaknesses of current network languages have encouraged the development of a new network language intended to be particularly appropriate to biological modeling. This language will be named ALEMBIC, an acronym for A Language for Expressing Models in Biology In Computers. The mathematical approach of the language is a nonlinear generalization of compartmental analysis, while the implementation is through a macrotranslator that produces MLAB programs as output.

Significance for Biomedical Research: Creation of complex models is much easier in ALEMBIC than in MLAB. The usual progression in modeling is from an analytical model that can be analyzed on paper to a more complex model that is to be analyzed with MLAB, and finally to a model that is too complex to be conveniently expressed in MLAB. While this final class of models is too complex to be used for data fitting, it provides a workbench on which to test the validity of simplifications from reality, which are ordinarily unexamined because to do so would be too time-consuming.

Progress in FY83: A bare-bones ALEMBIC translator has been programmed and tested on a variety of nontrivial problems, including examples from enzyme kinetics, ligand binding equilibria, and membrane

transport. The syntax for the full language has been outlined. A working user's manual is in development.

Future Course: The completion of the ALEMBIC translator is a major project whose completion will be a matter of several years. However, in FY84 considerable progress should be achieved. The user's manual will be extended to include not only specification of the syntax, but also a compendium of relatively elaborate examples that call upon the full power of the language.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00033-07 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (in characters or less. This must fit on one line between the borders.) Analysis of Coupled Transport and Biochemical Kinetics		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) P. RUDOW Expert LAS DCRT		
COOPERATING UNITS (if any) Medical College, University of Virginia; LB, NHLBI		
LABORATORY Laboratory of Applied Studies		
SECTION Applied Mathematics Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANYEARS 0.45	PROFESSIONAL* 0.30	OTHER* 0.15

Analysis of Coupled Transport and Biochemical Kinetics

This project investigates two fundamental problems in biology: the kinetics of enzymes located in cell membranes, and the thermodynamics of bioenergetic mechanisms in mitochondria. Mathematical analysis, simulation on digital computers, and numerical solution of nonlinear algebraic and differential equations are the main tools in these investigations. While these problems are diverse in their biological background, they all share in a common basis of mathematical and physical content in the role played by conservation laws and in the mathematical methods involved in their resolution.

- The Kinetics of Enzymes in Membranes

Background and Objectives: Studies of the mechanism of membrane transport and energy transduction by enzymes in membranes are generally less conclusive than studies of the mechanisms of isolated enzymes. This uncertainty arises because it is difficult both to manipulate the environment of the interior of a

biological membrane and to measure responses there. The objective of this project is to determine the extent to which the actual organization of membrane-associated, enzyme-catalyzed processes can be correctly inferred from the application of models, either detailed or phenomenological, to the kinds of experimental measurements currently made.

Significance for Biomedical Research: Studies of membrane-associated enzymes, such as those of mitochondria, for example, are made by measuring external concentration changes, from which one attempts to infer the biochemical mechanism. This process is evidently unreliable, as witnessed by a decades-long controversy over almost every detail of the mechanism. A consequence of our work is to suggest strongly that this lack of reliability is intrinsic. It is a result of incompatibility between the essentially macroscopic nature of the experimental observations, on the one hand, and the molecular character of the questions that are posed, on the other hand. For this reason, the problem is not to be resolved by performing yet another experiment of the kinds currently popular, no matter how ingenious.

Progress in FY83: One widely used alternative to the approach described above is to seek a phenomenological description of these systems using classical nonequilibrium thermodynamics. The two fundamental premises of this technique, termed linearity and reciprocity, have been shown to lack generality, and, indeed, to be specifically inapplicable to systems in which chemical reactions are important.

The manuscript describing experimental work in this area has been submitted and is under review. A second manuscript detailing the inappropriateness of nonequilibrium thermodynamics for characterizing this class of biological systems has been completed, and will be submitted shortly.

Future Course: The goal for FY83 will be to examine the incremental response of nonlinear reaction-diffusion systems that are maintained in a far-from-equilibrium stationary state. Because the important examples are all nonlinear, numerical rather than analytical methods will be needed.

• Thermodynamics of Bioenergetic Systems

Background and Objectives: The mechanism by which the generally reduced components of nutrients are oxidized in mitochondria is still elusive, although most of the components of this pathway have been identified. The membrane association of the components makes it difficult to proceed in the usual biochemical manner of molecular dissection and reconstitution. Most experimental studies are made on systems that are quite structurally complex. Nevertheless, interest focuses on the usual biochemical question: What is the sequence of molecular forms involved in the bioenergetic pathway? The role of the electron donor, ubiquinone, in this pathway is the particular object of our interest in this project.

Significance for Biomedical Research: An understanding of the mechanism of the central energy-yielding process of living organisms is clearly essential. Thermodynamic analysis has shown that the accepted explanation for the phenomenon of oxidant-induced reduction of cytochrome b by ubiquinone in the presence of antimycin cannot be correct. Presentation of a sound physical basis for analyzing multi-electron transfer reaction will assist many groups working on this problem who have previously accepted an invalid argument.

Progress in FY83: The manuscript describing this work has been completed and has undergone external review by leading workers in the field. It will be submitted shortly.

Future Course: This project is essentially complete. However, an effective basis for collaboration having been established, subsequent projects are anticipated.

Publications and Abstracts:

- Bunow, B.: All things flow and change. *Proc. Wash. Acad. Sci.* 72: 43-60, 1982.
- Bunow, B.: Cellular Enzymology: The steady-state kinetics of compartmentalized enzymes. *Journal of Theoretical Biology* 84 611-627, 1980.
- Bunow, B., and Mikulecky, D.C.: On the feasibility of using flux measurements to distinguish among active transport models. *Polish Winter School of Membrane Transport* (in press).
- Kernevez, J.P., and Bunow B.: Numerical exploration of bifurcating branches of solutions to reaction-diffusion equations describing the kinetics of immobilized enzymes. In Abi, E., Glowinski, R., Lascaux, P., and Veyssiere, H. (Eds.): *Numerical Methods for Engineering* Paris, Dunod, 1980, pp. 65-79.
- Kernevez, J.P., Joly, G., Duban, M.C., Bunow, B., and Thomas, D.: Self organization in enzyme systems. *In: Novosibirsk Colloquium 1978* Novosibirsk, Nauka, 1982, pp. 257-271.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00010-07 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Mathematical and Computational Methods for Solving Nonlinear Equations		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and outside affiliation) Richard T. Shrager Research Mathematician LAS DCRT		
COOPERATING UNITS (if any) HFD, CDC; DD, NIADDK; LB, NHLBI; IR/CM, IR/MD, NHLBI Cattedra Di Chimica e Biologica, U. of Milan, Milan, Italy; Univ. of MD., Computer Science Department		
LAB/BRANCH Laboratory of Applied Studies		
SECTION Applied Mathematics Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, MD 20205		
TOTAL MANYEARS 0.85	PROFESSIONAL 0.70	OTHER 0.15

Mathematical and Computational Methods for Solving Nonlinear Equations

Methods are developed for solving nonlinear equations frequently encountered at NIH. These equations are usually encountered in the context of constrained nonlinear least squares problems or in the numerical solution of nonlinear differential equations. Related problems, such as asymptotic error analysis and the efficient treatment of sparse matrix systems, are also considered.

Progress in FY83: A rapid, robust root finder has been developed and coded, and a revised manuscript describing the technique is being resubmitted to a journal. A new function minimizer is being coded by guest worker Behrooz Kamgar-Parsi for eventual inclusion in the MLAB system. A critique of a widely-cited method for differentiating spectroscopic data has been accepted for publication by the journal that originally published the method. A program has been written in the formal language REDUCE to compute exact coefficients of certain digital filters, which are used on laboratory computers that collect laboratory data online.

Circular dichroism measurements are being processed by singular value decomposition (SVD) methods. The objective is to clarify the mechanism by which calmodulin is altered by calcium and magnesium. This SVD method, developed at LAS in FY82, also is being used independently by two other laboratories in NHLBI. Some painstaking curve-fitting work was provided to

the Liver Unit of DD, NIADDK along with advice on which derived quantities were reliable. The objective of this project is to determine if faulty liver metabolism was responsible for increased GABA levels in rabbits with hepatic failure. A paper describing this effort has been accepted by *Hepatology*. In a paper with Drs. Setty and Hendler, now revised and accepted by *The Biophysical Journal*, a model of external and internal binding of Tetraphenyl Phosphonium (a membrane-potential probe) by bacteria was developed to show that the most likely distortions in membrane-potential measurements could be eliminated by a simple calibration. A paper describing a numerical procedure for generating a continuous hemoglobin-oxygen saturation curve while accounting for PO₂, PCO₂, pH and 2-3 DPG over a physiological range has been revised and published.

Proposed Course: In FY84, the calmodulin project should be completed, the function minimizer should be extended to handle linear constraints, and the new root finder will be installed in MLAB. A paper describing the root finder will be given at the 1983 SIAM Fall Meeting. Software, either imported or locally developed for the solution of nonlinear differential-algebraic systems, will be investigated; and the noise handling capacity of the SVD-titration analysis method will be examined.

Publications and Abstracts:

- Ferenci, P., Covell, D., Schafer, D.F., Waggoner, J.G., Shrager, R., Berman, M., and Jones, A.E.: Metabolism of the inhibitory neurotransmitter-aminobutyric acid in a rabbit model of fulminant hepatic failure. *Hepatology* (in press).
- Setty, O.H., Hendler, R.W., and Shrager, R.I.: Simultaneous measurement of PMF, delta pH, delta psi, and H₂O ratios in intact E. Coli. *Biophys. J.* (in press).
- Shrager, R.I.: Analysis of optical spectra by SVD. *SIAM 1983 National Meeting* (in press).
- Shrager, R.I.: Some pitfalls in the use of derivative spectra. *Photochemistry and Photobiology* (in press).
- Shrager, R.I.: SVD as a description of chemical titration. *SIAM 30th Anniversary Meeting*, Stanford University, California, July 19, 1982.
- Winslow, R.M., Samaja, M., Winslow, N.J., Rossi-Bernardi, L., and Shrager, R.I.: Simulation of continuous blood O₂ equilibrium curves over physiological pH, DPG, and PCO₂ range. *Journal of Applied Physiology* 54(2):524-529, 1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00045-05 LAS
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) The Solution of Reaction-Diffusion Systems in Biology		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliations) M. Bieterman Staff Fellow LAS DCRT		
COOPERATING UNITS (if any) J.E. Fletcher, Research Mathematician LAS DCRT IPST, Univ. of MD		
LAB BRANCH Laboratory of Applied Studies		
SECTION Applied Mathematics Section		
INSTITUTE AND LOCATION DCRT NIH, Bethesda, MD 20205		
TOTAL MAN YEARS 1.95	PROFESSIONAL 1.80	OTHER 0.15

Numerical Approximation Techniques for the Solution of Reaction-Diffusion Systems in Biology

Adaptive numerical methods, which were previously developed in LAS, have been improved and applied to solve systems of partial differential equations describing general reaction-diffusion processes in one space dimension. These methods are implemented in the program FEMOL1, which is available on the NIH IBM System 370 and DECsystem-10. FEMOL1 features automatic adjustment of the time and space discretizations during the course of the computations. These adjustments are effected in order to adapt to local problem characteristics and to control the discretization errors in an efficient manner.

The study of numerical techniques for time-dependent differential equations used to model reaction-diffusion processes has primarily consisted of the further development, analysis, and application of adaptive finite element methods. Adaptive numerical methods differ from conventional schemes in that information or feedback, which is gathered during a problem's solution, automatically is used to improve the accuracy and efficiency of the computations. Programs implementing such methods are valuable tools for the scientist examining the roles of physicochemical or biological parameters in model systems, because the roles can only be seen when the computed numerical solutions are sufficiently accurate. For a fixed set of model parameters, several applications of a conventional program with different input discretizations and numerical parameters are usually required to

guarantee solution accuracy. With a reliable adaptive method, the probability that sufficiently accurate answers are obtained in a single application of the program is high, as most decisions concerning appropriate discretizations and numerical parameters are made and carried out internally by the program.

Progress in FY83: The program FEMOL1 has been enhanced in several ways. Machine independence has been increased and a sophisticated package of subroutines has been added, making FEMOL1 independent of IMSL and other subroutine libraries. An arbitrary number of nonlinear partial differential equations, which may include nondominant, convective transport terms, can now be handled. Computational efficiency has been increased by incorporating a different discretization strategy in the adaptive procedure. Less user-supplied input is required, making the program easier to use.

FEMOL1 has been applied to models of oxygen transport, population ecology, population genetics, signal transmission in nerves, and physicochemical systems with strongly temperature-dependent kinetics. Many published benchmark tests for these and other models show the effectiveness of the adaptive solution approach.

Investigations of adaptive finite element methods have led to the design of a much improved algorithm for automatic space-mesh modification. With this algorithm, accurate information about solution characteristics is obtained via computable estimates of certain "local" quantities. This information is assimilated and monitored at an appropriate "global" level, and the evolving patterns, which are predicted via the many global levels, are used in deciding when and how a new space mesh should be constructed.

Proposed Course: The study of numerical techniques for the solution of partial differential equations, which model systems that describe or affect biological processes, will proceed in three directions. First, assistance will be given to DCRT investigators and other NIH scientists who need to use or obtain PDE software.

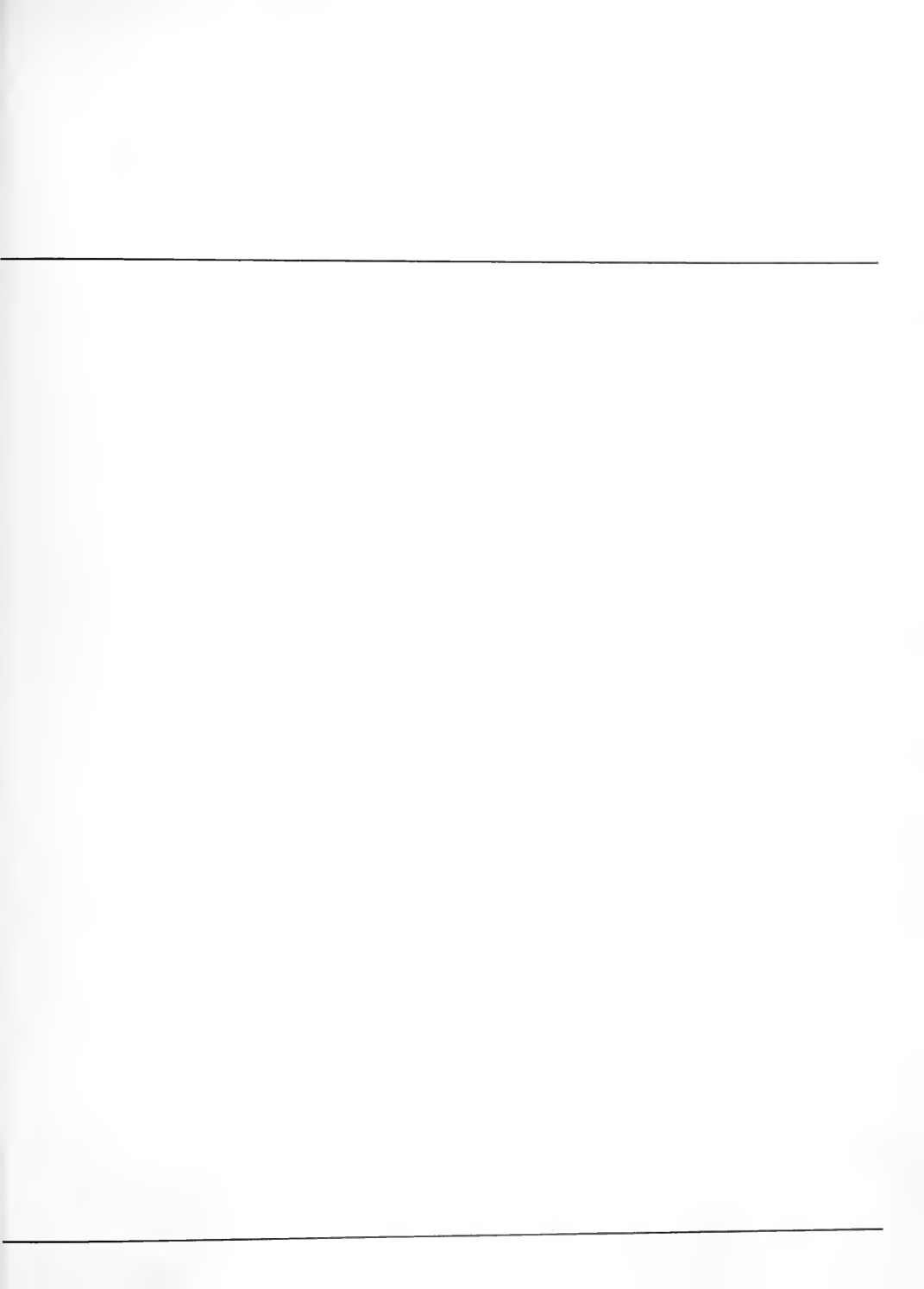
Second, adaptive numerical methods for reaction-diffusion systems will be extended, analyzed, and further implemented. Envisioned extensions include the capabilities to handle strong nonlinear coupling of higher solution component derivatives and more general boundary conditions. Also, preliminary studies of extensions of the present methods to two space dimensions will be made.

Third, mathematical modeling and numerical analysis of subsurface contaminant transport will be initiated. The diffusion and convection of hazardous chemicals through fractured rock and porous media are difficult both to model and to solve via computer. Multiple chemical reactions, radioactive decay, and anisotropic hydrodynamic dispersion can lead to complex flow patterns, in which the principle mechanism of transport

varies from one region of space to another. Adaptive numerical methods, which automatically adjust to subsurface flow patterns, will be investigated for these problems.

Publications and Abstracts:

- Bieterman, M.: An adaptive method for reaction-diffusion equations in one dimension. SIAM National Meeting. Denver, Colorado, June 1983.
- Bieterman, M.: A Posteriori error estimation and adaptive finite element grids for parabolic equations. *Army Research Office Workshop on Adaptive Methods for Partial Differential Equations* (in press).
- Bieterman, M.: On using local solution information in a mesh modification strategy for time-dependent equations. NASA-ICASE Workshop on Grid Methods. Hampton, Virginia, September 1983.
- Bieterman, M., and Babuska, I.: The finite element method for parabolic equations, I. A posteriori error estimation. *Numerische Mathematik* 40:339-371, 1982.
- Bieterman, M., and Babuska, I.: The finite element method for parabolic equations, II. A posteriori error estimation and adaptive approach. *Numerische Mathematik* 40:373-406, 1982.



**PROGRAMS/PACKAGES STATISTICAL SOFTWARE
MLAB CURVE-FITTING NUMERICAL DERIVATIVES
TATISTICAL METHODOLOGY MEDICAL INFORMATICS
ATOR PACKAGE GRAPHICAL DISPLAYS LINGUISTIC
EDICALL LANGUAGE CLUSTER ANALYSIS DISCRETE**

Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

LSM activities can be divided into three areas: computation, consultation, and research.

Computation

A major part of LSM activity is the offering of statistical and mathematical systems/packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does support a system/package for the NIH community, it provides maintenance, documentation, instruction, and assistance for users to interpret the results.

Statistical Systems/Packages Support. During this year, the Statistical Software Section of LSM maintained the following program packages and programs:

- BMD, BMDP: Biomedical Computer Programs, UCLA.
- SPSS, SPSS-X, SCSS: Statistical Package for the Social Sciences, SPSS, Inc.
- SAS, SAS/GRAPH, SAS/ETS: Statistical Analysis System, SAS Institute, Inc.
- P-STAT: Statistical Package, P-STAT, Inc.
- IMSL: International Mathematical and Statistical Libraries, IMSL, Inc.
- MSTAT1: Collection of Mathematical and Statistical Programs, DCRT.

During the year BMDP and IMSL went through a major update. NIH served as a test site for both SAS82 and SPSS-X. Both systems will become production systems during the next fiscal year. The SSS staff answered over 7,500 calls for assistance, and taught a total of twelve courses on these systems/packages; two each on the SPSS and BMDP packages and eight courses on the SAS system.

The use of program packages continues to increase. The average accesses per month of all the statistical packages rose from around 45,000 during FY82 to over 63,000 in FY83. For the seventh year in a row, SAS experienced the largest increase of any of the packages. SAS averages over 54,000 accesses per month, up from 37,000 per month in FY82. The average number of accesses per month for SPSS--

around 4,600--was about the same as in FY82. The average combined accesses of the BMDP and BMD packages was 2,500, about the same as in FY82. As an example of a package used for specialized purposes, P-STAT averaged 20 accesses per month, down from 30 average accesses per month in FY82. The main programs and subroutines in MSTAT1 averaged 1,600 accesses per month, in contrast with 1,300 in FY82. Accesses to the IMSL package cannot be counted, but it is estimated that usage increased during FY83.

MLAB Support

The Biomathematics and Computer Science Section maintains the DECsystem-10 interpretive program MLAB, a package designed and implemented by BCS staff. During FY83, several hundred biomedical researchers at NIH used this package for modeling and graphical display tasks. MLAB is part of the NIH-funded Prophet system, the SUMEX-AIM system at Stanford University, and the NIH-EPA Chemical Information System. It has been distributed to various universities and research centers at their request. During FY83, BCS augmented MLAB in several areas. Numerical derivatives can now be specified for curve-fitting, allowing analysis of somewhat larger models. Several new mathematical operators were added. MLAB was modified to permit use of the color graphics facilities of OMNIGRAPH, and the facilities for graphical display of scientific text were enhanced. One advanced course and two introductory courses were taught for MLAB. One article and one puzzle feature on MLAB techniques appeared in *INTERFACE*. The second edition of the *MLAB Beginners Guide* is being printed, and will be distributed in FY84.

Support for the Unified Generator Package

This package, developed by a BCS staff member, generates IBM System 370 assembly language programs. Maintenance was performed on the package to accommodate the upgrade from 3330 to 3380 disk drives and the system change from the G Assembler to the F Assembler. The bucket overflow algorithm for the index generator was improved. As before, assistance was provided for users on request.

Support for Other Software

BCS continues to maintain certain special-purpose software and to assist users upon request. The PROLOG package, which the Japanese government has adopted as a basis for their fifth-generation computer project, is designed for analysis of nonnumerical data by aggregation of procedural rules. It has been used in LSM for linguistic research. A program developed by BCS for interactive construction of an index for a document file has been supported. Various LSM-created programs for analysis and reconstruction of biological shapes using the symmetric axis method have been supported. BCS staff supported SAS/GRAPH maintenance, especially for the Calcomp plotter interface and the TSO command processor.

Consultation

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are successful and are brief precisely because there is a known answer to the question posed. Other consultations involve extensive time and statistical/mathematical/computer science research as well. LSM consultations in FY83 were of the following types:

- Mathematical, statistical and computer science advice with limited computer use (5 percent)
- Mathematical or statistical advice with considerable computer use (55 percent)
- Computational advice alone (40 percent).

The large computer use in these figures results from the continued availability and use of general purpose statistical and mathematical packages like SAS and MLAB. These percentages are unchanged from last year.

The diverse nature of LSM consulting is indicated by the projects and activities listed below.

Clinical Research, Patient Care, Epidemiology

Allergen Treatment for Ragweed Hayfever. P. Turkeltaub (BB/DPB). The safety and efficacy of

allergen treatment for ragweed and hayfever was studied by analysis of clinical data. LSM provided statistical and computational assistance for nonparametric tests for ordered alternatives, stepwise multiple comparison procedures, and analysis of covariance.

Effects of Age on Taste Sensitivity. B. Cowart and J. Weiffenbach (NIDR/DSB). Ordered sequences of taste samples are presented to human subjects for evaluation. LSM developed a new statistical methodology for pairwise comparison of evaluations of ordered concentrations, for assessment of decreased taste sensitivity with age.

Cancer Survival Studies. R. Wesley (NCI/DCT/BRB). LSM assisted in computer generation of graphical displays, involving Kaplan-Meier survival curves for evaluation of clinical data.

Hypertransfusion and Blood Constituents. P. Gascon (NHLBI/IR/OD). LSM gave statistical consultation on a study of the consequences of hypertransfusion for several blood constituents. Comparisons were made using nonparametric tests between normal controls and patients having one of several diseases, each requiring high numbers of transfusions as part of the disease treatment.

Laboratory Investigation

Receptor Characterization. M. Bissonette (NIADDK/DD). Models for the characterization of secretin receptors in rat pancreatic acini in terms of receptor number and receptor affinity were studied. LSM continued to assist in simultaneously curve-fitting nonlinear models to experimental data.

Peptide Potencies. D. J. Goldstein (NHLBI/HE). The effect of four naturally occurring peptides of the kinin family (bradykinin, lysylbradykinin, methionyllysylbradykinin, and polisteskinin) in reversing the inhibitory effect of morphine and metenkephalin on the electrically simulated guinea pig ileum longitudinal muscle-myenteric plexus preparation was studied. LSM assisted in using parallel line assay techniques to compute the relative potencies as well as the ED50's

(concentration required to produce a 50 percent reversal of the opiate-induced inhibition) of the peptides. A coauthored manuscript reporting the results has been submitted to *Science*.

Effects of Oxotremorine on Whole Body Tremor in Chronic Drug-treated Rats. M. Goldman (NINCDS/ET). Rats were injected twice daily for 30 days with saline, atropine, amitriptyline, thioridazine, imipramine, d-amphetamine, or nomifensine. Seventy-two hours after the last dose each animal was injected subcutaneously with 0.1 mg/kg oxotremorine. The proportion of animals displaying a supersensitive response (moderate to severe whole body tremor for at least three single minute intervals from 11-15 minutes) to oxotremorine was recorded. LSM assisted in computing confidence intervals for the proportions, using Fisher's exact test for 2x2 tables.

Basal Membrane Thickening in Galactosemic Rats. P. Kador (NEI/LVR). Basal membranes were analyzed in normal rats, galactosemic rats, and galactosemic rats treated with aldose reductase, using retinal capillary images from electron micrographs. This study is related to clinical management of eye complications resulting from diabetes. LSM assisted in computer generation of graphical displays and measurement of image features.

Cholesterol Levels in Swine. J. Cupp and H. Kruth (NHLBI/IR/EA). Effects of high cholesterol diets on swine are assessed by sacrificing the animals and measuring atherosclerotic pathology. LSM provided statistical advice in the sampling design and analysis of a linear model that adjusts for the effects produced by using experimental animals from the same litter.

Differential Binding of Synthetic Retinoids to Beta-lipoproteins. E. Gross (NCI/DCDB). Experiments show that different retinoids (Vitamin A derivatives used in treatment of dermatologic disease) are associated in different degrees with beta-lipoproteins; these results have implications concerning the absorption, distribution and metabolism of the drugs. LSM assisted in the use of SAS/GRAPH to prepare graphical presentations of these results.

DNA Sequence Analysis. P. Senepathy (NIADDK/LEP). Various natural DNA sequences are compared to

assess biochemical features of sequence data. LSM assisted in the preparation of graphical displays using MLAB that show cleavage points of sequences under the action of several different enzymes.

Kidney Function Modeling. C. DeLisi (NCI/LTB). Aspects of kidney function are modeled by large systems of ordinary differential equations. LSM provided advice in formulation of the models and in using MLAB for generation of numerical solutions and for curve-fitting.

Cooperative Binding of Polymers. J. Cohen (NIADDK/LCP). Binding of n-mers was measured using NMR data. LSM provided assistance in formulation and analysis of a mathematical model.

Brain Tissue Analysis. S. Kumins (NICHD/ERRB). Mixtures of damaged and undamaged enkephalin bind differentially to specific brain tissue sites. LSM provided assistance in formulation and analysis of mathematical models using MLAB.

Computer Research and Technique Development

Computer Analysis of Two-Dimensional Gel Electrophoresis Images. M. Miller (NCI/DCCP). LSM provided advice on the use of Fourier analysis filtering techniques for computer enhancement of protein spots on gel images.

Comparison of Dental X-Ray Images. R. Webber (NIDR/CIBI). LSM provided advice on a method for better control of computer image positioning, to reduce problems associated with comparisons between related images.

Probability Models for Fibrinogen Chains. G. Crabtree (NCI/DCBD/LP). LSM assisted in developing probability models to account for the presence or absence of introns in the three present-day fibrinogen chains, as derived from a single or double ancestral gene. The model fitting used maximum likelihood and a set of chi-square statistics.

Schematic Figure Generation. R. Hiller (NEI/BE). LSM provided a computer program for generating

schematic diagrams using four overlapping circles. The circles are positioned so that the areas of the 15 regions of overlap approximate values supplied by the user. These diagrams are being used as visual aids in presentation of data involving four types of senile cataract disease.

Fibrinogen Binding Displays. M. Lewis (DRS/BEI). LSM assisted in preparation of three-dimensional graphical displays and contour maps of data associated with binding of fibrinogen to plasminogen, using MLAB.

Graphical Display of Hormone Levels. N. Vieira (NICHD/NPMB). LSM assisted in preparation of MLAB DO files for continuing production of graphs showing hormone levels, including use of spline approximations and generation of error bars.

Research Projects

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00001-12 LSM
PERIOD COVERED October 1, 1982 through September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the brackets.) Automated Data Processing of Medical Language		
PRINCIPAL INVESTIGATOR (Use other prebiological personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation)		
M. G. Pacak	Supv. Computer Systems Analyst	LSM DCRT
A. W. Pratt	Director	OD DCRT
G. Dunham	Computer Programmer	LSM DCRT
S. Harper	Computer Programmer	LSM DCRT
D. Henson		DRCCA NCI
LABORATORY Laboratory of Statistical and Mathematical Methodology		
SECTION Medical Information Science Section		
INSTITUTE AND LOCATION DCRT, NIH, Bldg. 12A, Room 3045, Bethesda, Maryland 20205		
TOTAL MANYEARS 1.5	PROFESSIONAL 1.5	OTHER

Automated Data Processing of Medical Language

Research was continued on compositional morphosemantic analysis of medical terms derived from Greek and Latin. A methodology was developed for automated morphosemantic segmentation and semantic interpretation (paraphrasing rules) of medical compound words derived from Greek and Latin that denote surgical procedures. Of primary importance is the construction of a lexicon of potential morphosemantic constituents that associate with each entry a semantic category used in SNOP and its semantic interpretation in medical English. The

preparation and use of Greek-Latin morphosemantic constituents result in a net saving in required storage space and an increase in the lexicon's interpretation power, because it is possible to derive semantic interpretation from words that are not contained in a dictionary in their full form.

The morphological analysis (stemming algorithm), which consists of the identification of the word root and the automatic selection of morphological word variants from inverted file entries, was used successfully in an end-user interface to NLM's CATLINE book catalogue file.

Collaboration on the Clinical Information Utility continued with the Laboratory of Pathology, NCI, and the DCRT Data Management Branch to maintain and improve the data base of Clinical Center surgical pathology reports.

The automatic encoding system provided by MISS computes a representation of the summary diagnoses of the surgical pathology report as written by the pathologist, in a language based on the vocabulary of the Systematized Nomenclature of Pathology (SNOP-NIH). Statements in this representation language convey the site and tissue of the specimen, the specific morphologic and histopathologic diagnoses, and etiologic agents involved in a diagnosis.

Continued collaboration with Dr. Donald E. Henson, NCI (Division of Resources, Centers, and Community Activities, Organ Systems Branch), has been basic to this work. We have begun work on specific areas of the dictionary along the lines established for the lymphoma vocabulary with interested specialized pathologists including Dr. Elaine S. Jaffe, NCI (Division of Cancer Biology and Diagnosis, Laboratory of Pathology, Hematopathology Section).

Steps were taken to create a comprehensive lexicographic data base relating the body of medical nomenclature and vocabulary to itself in various logical ways, and to existing structuring or coding systems. The goals are: to produce the semi-automatic display of significant relationships of one dictionary system to another, to merge dictionaries, and to maintain and extract special purpose microglossaries necessary for

medical language processing and data base organization.

A paper, "Three Solutions to Problems of Categorized Medical Nomenclatures," is in preparation.

Publications:

Norton, L. M., and Pacak, M. G.: Morphosemantic Analysis of Compound Word Forms Denoting Surgical Procedures. *Methods of Information in Medicine*. 22: 29-36, 1983.

other on the cumulative distribution function of the central angles of Voronoi regions, were used to evaluate models.

Future work will involve using the elastic ball model and finding the resulting parameters for other retinal data (e.g., blue cones at different locations in the retina) and all cones (i.e., red sensitive and green sensitive as well as blue sensitive).

Publications:

Shapiro, M.: A note on Lee and Schacter's algorithm for Delaunay triangulation. *International Journal of Computer and Information Sciences*. 10 (6): 413-418, 1981.

Yar, I., and Shapiro, M.B.: A quantitative study of the Electroencephalographic Response to Levodopa treatment in Parkinsonian patients. *Clinical Electroencephalography* 14 (2): 82-85, 1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00008-09 LSM	
PERIOD COVERED October 1, 1982 through September 30, 1983			
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Cluster Analysis			
PRINCIPAL INVESTIGATOR (Last other professional personnel on salary unit page) (Name, title, laboratory, and institute affiliation) M. B. Shapiro Research Mathematician LSM DCRT			
COOPERATING UNITS (if any) F. de Monasterio Head LVR NEI S. Schein Expert LVR NEI			
LAB BRANCH Laboratory of Statistical and Mathematical Methodology			
SECTION Statistical Methodology Section			
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS 1.0	PROFESSIONAL 1.0	OTHER	

Cluster Analysis

The main objective of this project is the application of computer cluster analysis and related methods to NIH researcher problems.

Nearest neighbor algorithms based on the latest published research and extensions to it were developed and tested.

Algorithms for analyzing spacial point patterns were developed for testing patterns of retinal cones for regularity.

The first phase of the work on the distribution of blue sensitive cones in the retina was completed and a paper, "Regularity and Structure of the Spatial Pattern of Blue Cones of Macaque Retina," was submitted for publication in the Applications Section of the *Journal of the American Statistical Association*. The final model developed considers each cone as an elastic ball, with a hard core and soft surrounding shell. Models based on disordered triangular and square lattices were rejected. Two statistics, one based on the cumulative distribution function of interpoint distances and the

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00009-09 LSM	
PERIOD COVERED October 1, 1982 through September 30, 1983			
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Research Topics in Computer Science			
PRINCIPAL INVESTIGATOR (Last other professional personnel on salary unit page) (Name, title, laboratory, and institute affiliation) C. D. Knott Computer Specialist LSM DCRT			
COOPERATING UNITS (if any) None			
LAB BRANCH Laboratory of Statistical and Mathematical Methodology			
SECTION Biomathematics and Computer Science Section			
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS 0.3	PROFESSIONAL 0.3	OTHER	

Research Topics in Computer Science

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is very useful, because such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

Currently, a study of hashing storage and retrieval methods is underway. This has resulted in an analysis of the performance of the hashing methods that resolves collisions using direct-chaining with and without coalescing lists. Progress has been made on analyzing the insertion cost for direct-chaining, involving the computation of a hard-to-derive covariance.

The object of this project is to develop theoretical bases for new computer methods that will expand and improve the use of computing in biomedical computation. The methods used are the application of known algorithms and the development of new pertinent theorems involving combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern.

Concurrently, an exhaustive survey of storage and retrieval methods is underway. This includes the recently-introduced k-d tree method. Various improvements and refinements in both the algorithms and their analysis are being studied.

Routines to store, retrieve, and delete items in a hash table that employs direct-chaining with and without coalescing lists have been prepared. An analysis of these algorithms has been recently completed and the results are to be published. Further analysis is underway.

Publications:

Knott, G. D.: Direct Chaining with Coalescing Lists. *Journal of Algorithms* (in press).

Knott, G.D.: Fixed-Bucket Binary Storage Trees. *The Journal of Algorithms*. 3: 276-287, 1982.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00011-09 LSM
PERIOD COVERED October 1, 1982 through September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Discrete Mathematics and Applications		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) G. Hutchinson Supv. Res. Mathematician LSM DCRT		
COOPERATING UNITS (if any) None		
LAB/BRANCH Laboratory of Statistical and Mathematical Methodology		
SECTION Biostatistics and Computer Science Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.4	PROFESSIONAL 0.4	OTHER

Discrete Mathematics and Applications

Inclusion relations between vector spaces and related problems concerning modules over rings were studied.

Preparation of scientific manuscripts by computer graphics methods using printer-plotters was investigated.

The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics, and graph theory), and to apply such methods to problems of biomedical research and computer science.

A study of algebraic structure possessed by submodules of module products $M \times M$ was begun. Preliminary findings include: construction of an axiomatic algebraic structure representing such relation algebras, construction of relation category analogs of these algebras, characterization of the subcategories of relations that are function graphs for these analogs, a number of special results showing that certain classes of abstract algebras are isomorphic to subalgebras of module relation algebras, a decision procedure for the identities satisfied in all module relation algebras in terms of certain simple divisibility properties of the ring of scalars, and a classification of rings determining when two different rings lead to the same identities for the corresponding module relation algebras.

In computer science, a DECsystem-10 program was written and tested for conversion of the scientific manuscript input language previously developed in this project into the input language used by TeX (a computer manuscript system developed at Stanford University that has been adopted by the American Mathematical Society). Further tests of TeX have been performed, and LSM assisted the DECsystem-10 systems staff in their effort to implement the most recent version (TeX82). Procurement of the Tektronix 4114 graphical display terminal is not yet completed.

Proposed Course: Study of module theory will continue in the areas indicated above.

Computer software to generate scientific manuscripts will be developed. It is expected that Tektronix 4114 procurement will be completed and development of computer manuscript output will begin late in FY83. Use of the IBM 6670 Information Distributor as an output device for generation of scientific manuscripts will also be investigated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00013-09 LSM	
PERIOD COVERED October 1, 1982 through September 30, 1983			
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Multivariate Statistical Analysis			
PRINCIPAL INVESTIGATOR (Last name, professional personnel on subsequent pages) (Name, title, laboratory, and mailing affiliation) J. E. Mosimann Chief, LSM LSM DCRT			
COOPERATING UNITS (if any) J. N. Darroch Flinders University, Adelaide, Australia M. V. Ratnaparkhi Associate Professor, Wright State University, Dayton, Ohio			
LAB BRANCH Laboratory of Statistical and Mathematical Methodology			
SECTION Office of the Chief			
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS 0.3		PROFESSIONAL 0.3	

Multivariate Statistical Analysis

The objective of this project is the study of multivariate ratios or proportions.

Study continued on multivariate statistical methods (size-shape methods) for analyzing ratios that follow a multivariate lognormal distribution. A paper on discriminant functions based on shape alone (with J. N. Darroch) is under revision. The application of these methods to quality control of inbred stocks of laboratory mice was undertaken (with H. Hoffman). These discriminant methods enable the early detection of contamination of inbred strains. A rather complete review of size and shape analysis was prepared, and accepted, for the *Encyclopedia of the Statistical Sciences*. Additionally, various data sets of use in size and shape studies, which formed the basis for previous studies, have been edited and collected as a resource for test analyses. Additionally, specialized programs for the analysis of size and shape data have been developed. The principal investigator participated in the International Workshop on Functional and Structural Relations and Factor Analysis at the University of Dundee (Aug. 24-Sept. 6, by invitation only) and participated in a subsequent open meeting on the subject on September 7-9, 1983.

Publications:

DeBias, A. L., Ratnaparkhi, M. V., and Mosimann, J. E.: Estimation of the number of monoclonal hybridomas in a cell fusion experiment. In Yunakis, H. V., and Langone, J. J. (Eds.): *Immunochemical Techniques: Methods in Enzymology*. New York, Academic Press, 1983, pp. 36-39

Mosimann, J. E.: Size and Shape Analysis. In Johnson, N. I., Kotz, S., and Read, C. B. (Eds.): *Encyclopedia of Statistical Sciences*. John Wiley and Sons, Inc. (in press).

Mosimann, J. E.: Discussion of Professor Aitchison's paper *Journal of the Royal Statistical Society B*, 44 (2) 168-170, 1982

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT 00019-06 LSM	
PERIOD COVERED October 1, 1982 through September 30, 1983			
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Linear Methods in Statistics			
PRINCIPAL INVESTIGATOR (Last name, professional personnel on subsequent pages) (Name, title, laboratory, and mailing affiliation) J. D. Malley Mathematical Statistician LSM DCRT			
COOPERATING UNITS (if any) None			
LAB BRANCH Laboratory of Statistical and Mathematical Methodology			
SECTION Statistical Methodology Section			
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS 0.6		PROFESSIONAL 0.6	

Linear Methods in Statistics

Linear methods in statistics, as applied to biomedical data analysis, continue to be studied. The study of optimal linear model estimates for variance component estimation continues to be an area of investigation. An extensive study of repeated-measures experiments was begun, and the results will be a monograph on the unified exposition of the problem as well as to present an exact multivariate alternative analysis. Further, linear, nonparametric, multivariate methods have also been outlined. Additionally, a new approach to the problem of describing and characterizing multivariate dependence structures has been presented that ties the practical problem of studying dependence to a geometric framework.

Publications:

Malley, J. D.: Statistical and algebraic independence. *The Annals of Statistics* 11 (1): 341-345, 1983

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT 00047-05 LSM	
PERIOD COVERED October 1, 1982 through September 30, 1983			
TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders.) Nonnumerical Programming Techniques and Applications			
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Lewis H. Norton Research Mathematician LSM DCRT			
COOPERATING UNITS (if any) None			
LAB/BRANCH Laboratory of Statistical and Mathematical Methodology			
SECTION Biomathematics and Computer Science			
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS 0.4	PROFESSIONAL 0.4	OTHER	

Nonnumerical Programming Techniques and Applications

The special purpose programming language PROLOG is quite different from other languages, and optimum use of it requires using new techniques and abandoning ones used with other languages. PROLOG programs that analyze medical terms in terms of their constituent morphemes were refined and extensively tested. Additional efforts in text analysis and other areas also involved the use of PROLOG. Papers were prepared for publication.

Research on this project has continued to focus on the use of the special-purpose programming language PROLOG. In a computational linguistics project, PROLOG programs that analyze medical terms denoting inflammations and surgical procedures were further refined and tested. The analysis was performed in terms of the constituent morphemes of the terms, and required the compilation of an extensive lexicon of such morphemes. Output from the program was used to determine morphosemantic distribution patterns and their relative frequencies within the corpus of terms, as well as the semantic interpretations associated with the more common patterns. A paper on the results of this work for the domain of surgical procedure terminology was written.

Additional efforts involving PROLOG included research in the area of text analysis, where a paper based on earlier work was revised for publication, and where text analysis techniques reported in the literature were

implemented in PROLOG to increase comprehension of both the techniques and the programming language. Other small-scale projects were done, mainly to explore other properties of PROLOG. PROLOG is quite different from other programming languages, and optimum use of it requires abandoning many preconceived programming methodologies.

We are hoping to obtain a newly-released version of PROLOG for microcomputers, in order to broaden our investigations into the uses of this language.

During this reporting period, some further work was performed on a project investigating the frequencies of terms used in surgical pathology summary diagnoses. In particular, data was collected on changes in word frequencies over time, and frequencies of multiple use of terms in the same summary diagnosis. Much of the software used was created using the Unified Generator Package.

Publications:

Norton, L.M., and Pacak, M.G.: Morphosemantic Analysis of Compound Word Forms Denoting Surgical Procedures. *Methods of Information in Medicine* 22: 29-36, 1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT 00079-03 LSM	
PERIOD COVERED October 1, 1982 through September 30, 1983			
TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders.) Topics in Geometry and Analysis			
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) M. A. O'Connor Staff Fellow LSM DCRT			
COOPERATING UNITS (if any) C. R. Merrill Senior Research Scientist LGCB NIH D. Goldman Clinical Associate LGCB NIH			
LAB/BRANCH Laboratory of Statistical and Mathematical Methodology			
SECTION Biomathematics and Computer Science Section			
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205			
TOTAL MANYEARS 0.7	PROFESSIONAL 0.7	OTHER	

Topics in Geometry and Analysis

Improvements in accuracy and efficiency of identification and description of protein spots in two-dimensional gels were developed and coded. Analysis of general algorithms in relationship to existing edge detection and region segmentation techniques was undertaken.

Continuing research in the geometry of convex cones, the connection and Riemannian curvature tensor of the related isometric triangular Lie groups was calculated. Results on Einstein manifolds and cones were obtained. Previous parametrization of N-algebras was related to sectional curvature, and thus seen to be intrinsic.

The project objective is to develop mathematical and computational techniques using geometry and mathematical analysis, and to apply such methods to problems of biomedical research and computer science.

At this point, the eye is the most accurate and effective detection device for protein spots in two-dimensional electrophoretic gels. The edges of the spots can generally be well fit by parabolic segments. An algorithm has been developed to model parabolic fitting by the eye utilizing a "parabolic spatial second derivative" and other analogues of cues used by the eye. This has been coded as a Pascal program on a VAX computer. (This work is in collaboration with LGCB, NIMH.)

It is noted that the technique developed here in its actual implementation is closely related to the higher cortical organization proposed by Hubel and Wiesel for the visual system. Moreover, in its global approach, the algorithm is similar to the Hough transform, sharing geometrical description as a goal while not suffering susceptibility to local noise.

By developing alternate characterizations of some of the axioms, space for the algebras can be constructed as the intersection of hyperplanes and a sphere in an appropriate vector space. A unique (with respect to N-algebra isomorphism class) parametrization space is then obtained as the quotient of the subset of the vector space by a tensor product of two lower dimensional orthogonal groups. By evaluating canonical Riemannian geometry of a cone of generalized positive definite symmetric matrices with respect to a particular field of bases, one uses the standard diffeomorphism from the triangular group of a T-algebra onto its related cone to endow the Lie group with a left-invariant Riemannian metric that is isomorphic to the geometry of the cone.

Using this geometry on the Lie group, the connection and Riemannian curvature tensors were calculated. Calculation of certain sectional curvatures yields the alternate characterization described above for the N-algebra, and shows that this and hence the parametrization must be intrinsic. Further, it is shown that in at least the rank 3 case, a cone is determined by its curvature tensor. Contraction of the curvature to the Ricci tensor and calculation of i, j coefficient for i and j diagonal vectors yields that it equals a constant times the dimension of the i, j subspace, so that only products of the positive reals are Einstein spaces. The curvature tensor can be shown to generalize that found by C. L. Siegel for a type 1 Siegel domain built over the cone of positive definite symmetric matrices.

Publications:

O'Connor, M. A.: Invariant metrics on cones. *Proc of the Conference on Invariant Metrics and Holomorphic Maps*, Rome, Italy, Istituto di Alta Matematica F. Severi di C.N.R. Symposia Mathematica, Volume XXVI, London and New York, Academic Press, 1982

DEPARTMENT OF HEALTH AND HUMAN SERVICES, PUBLIC HEALTH SERVICE		PROJECT NUMBER	
NOTICE OF INTRAMURAL RESEARCH PROJECT		ZDI CT 90111-01 LSM	
PERIOD COVERED: October 1, 1982 through September 30, 1983			
TITLE OF PROJECT: <i>See chapters or use. (This must be on one line between the heading Nonparametric Statistics)</i>			
PRINCIPAL INVESTIGATOR: (List other professional personnel on subsequent pages.) Name: <i>See laboratory and institute affiliation</i>			
Gregory Campbell		Senior Staff Fellow	LSM DEPT
COOPERATING UNITS: (If any)			
None			
LAB BRANCH: Laboratory of Statistical and Mathematical Methodology			
SECTION: Statistical Methodology Section			
INSTITUTE AND LOCATION: DEPT, NIH, Bethesda, Maryland 20205			
TOTAL MANUSCRIPTS	PROFESSIONAL	OTHER	
0.5	0.5		

Nonparametric Statistics

Research is concentrated on several topics of nonparametric statistics. The study of nonparametric multiple comparisons has been initiated in FY83, with particular attention to the theoretical as well as computer simulated behavior of various procedures. The optimal selection of a sequence of items based on relative ranks with ties has been investigated. Thirdly, an evaluation of tests for correlated proportions with incomplete data has been undertaken.

Work has been initiated in FY83 in the area of methodology for nonparametric multiple comparisons. Evaluation of stepwise multiple comparison procedures has been done both theoretically and using computer simulations. Work is continuing in this area.

The optimal selection of a sequence of items based on their relative ranks with the possibility of ties has been investigated. A paper has been submitted for publication.

An evaluation of statistical tests has been undertaken for correlated proportions for incomplete data. A test based on the iterative maximum likelihood estimator is

being compared with several ad hoc procedures in an ongoing investigation.

Publications:

Campbell, G.: Asymptotic Properties of Several Nonparametric Multivariate Distribution Function Estimators Under Random Censoring. *Survival Analysis*. In Crowley, J., and Johnson, R. A. (Eds.): Institute of Mathematical Statistics Lecture Notes--Monograph Series. Haywood, California, 1982, pp. 243-256.

Campbell, G.: Optimal Selection Based on Relative Ranks of A Sequence with Ties. *Advances in Applied Probability* (in press).

Campbell, G., and Foldes, A.: Large Sample Properties of Nonparametric Bivariate Estimators with Censored Data. *Colloquia Mathematica Societatis Janos Bolyai. Nonparametric Statistical Inference*. Budapest, Hungary, 32: 103-121, 1980.



ENGINEERING SPECIALIZED COMPUTER SYSTEMS
ELECTRONIC DEVELOPMENT LABORATORY AUTOMATION
PROGRAMS MICROCOMPUTERS MICROPROCESSORS
SELECTED DISPLAY MOLECULAR GRAPHICS LABORATORY
ENGINEERING INSTRUMENT INTERFACES PICTURE ARCHIVING

Computer Systems Laboratory

Alan M. Demmerle, Chief

Clinical Research, Patient Care, Epidemiology

Computer Support for Flow Cytometry/Electronic Cell Sorters (FC/ECS) (NCI, NHLBI). This project provides support for the acquisition, display, and analysis of data from instruments in NCI and NHLBI: four Becton-Dickinson FACS-II and one Coulter MDADS FC/ECS. All five systems currently use Digital Equipment Corporation PDP-11 computers. Four systems use the RT-11 operating system to process data from one user at a time while one system uses the RSX-11M operating system to support multiusers and tasks simultaneously. The RSX-11M operating system, designed for high volume applications, was used to upgrade the I, NCI FC/ECS in FY83. This system features an LSI-11/23 microcomputer (satellite) that connects to an 11/24 minicomputer (host) via an interprocessor link. A FC/ECS operator interacts with the satellite for parameter entry and data acquisition, which is performed independently of the host. Once data is acquired, it is sent to the host where it is stored, displayed, analyzed, and results are printed or plotted.

Cardiac Scintillation Probe (CC, NHLBI). This nonimaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. The system can continuously derive parameters such as LV compliance, ejection fraction, filling and ejection rates, and various temporal relationships. The probe continues to be used to study the effects of nifedipine and verapamil on patients with asymmetric septal hypertrophy and coronary artery disease. The probe is also being used to monitor the left ventricle performance of patients in the Medical Intensive Care Unit.

Nuclear Medicine Computer Systems (CC). CSL has continued consultation and support for imaging systems in the Nuclear Medicine Department to assess their changing needs and to evaluate their increased requirements with a view toward their anticipated growth. This year four new viewing stations were installed. A system for single photon tomography was selected for purchase. A new camera interface (analog to digital converter system) was installed and is being

evaluated as a possible replacement for the four present camera interfaces. Investigation was initiated into a department-wide central picture viewing and storage system.

Medical Intensive Care Unit Patient Monitoring Computer System (CC). Dynamic events occurring within the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system. Capabilities of the system include data acquisition and analysis, medical recordkeeping, tabular and graphical data display, and feedback control as required in support of patient care and research protocols. The Facility contains a state-of-the-art catheterization laboratory with flexible computerized physiologic monitoring features, and a high resolution x-ray system with digital subtraction angiography capability. Of primary interest is the utilization of the Medical Intensive Care Unit's computer systems in the study of the etiology and therapy of septic shock.

The Biomedical Image Analysis Projects (NHLBI, NIA, NCI, NIADDK). These projects are oriented toward the development of general-purpose algorithms and techniques for image input (including digitization), image enhancement (including contrast enhancement), feature extraction (including edge detection, contour extraction, contour following, contour coordinate compression, and shape and texture analysis), three-dimensional representation, image reconstruction (including Fourier filtering, combining images, symmetrization), and other techniques of image processing and image reconstruction. The resultant general-purpose capability is being accomplished through work with a number of NIH researchers who encounter relatively similar classes of problems in unique individual settings.

Automated ECG Processing (CC). The Clinical Center's Heart Station was automated in FY81 with a computer system that provides online acquisition, analysis, storage, and retrieval of diagnostic electrocardiograms. The newest versions of the vendor's turnkey software and diagnostic criteria packages were installed recently, and the system was placed in routine clinical operation. As utilization of this system progresses, the medical staff will identify specific diagnostic criteria and statements that require

modification to provide compliance with NIH Heart Station standards for diagnostic electrocardiography. The ECG analysis package will then be modified as necessary to customize the ECG analysis process in order to satisfy NIH requirements.

Department of Rehabilitation Medicine Computer System (CC). This project involves the development of computer techniques in collaboration with the Department of Rehabilitation Medicine of the NIH Clinical Center. CSL has recommended computer techniques that can be used to automatically acquire anatomical and physiological information from patients, perform the required calculations on the data obtained, and display the necessary results to the medical staff. The automated techniques include the measurement of body forces (hand and ground reaction forces), electromyograms (electrical activity of the muscles), and body kinematics (the position and angles of the limbs and joints in space and time). An Automated Biomechanics Laboratory System that will provide these measurements was purchased in FY83. The computer part of the system will allow the medical staff to enter patient and staff data into a data base with computer generated forms displayed on a terminal screen. The system also will perform inquiries and generate reports using the accumulated data. In FY83, the physical space for the purchased system was designed, and the system was installed. The Automated Biomechanics Laboratory will begin operation with the start of FY84.

Positron Emission Tomography (PET) Facility (CC). CSL has developed an interim offline imaging computer to handle the substantial data analysis requirements of the users of the Nuclear Medicine PET Facility. A microcomputer link has been programmed to interface scintillation counter output to the offline computer. The PET scanner computer system has been expanded to include new peripherals to manage increased data flow.

Picture Archiving and Communication System (PACS) (CC). The purpose of this project is to develop a system to store and transmit medical images and to allow access to pictures representing different imaging modalities from a single viewing station. Such a system will draw on the latest technological developments in

the fields of data storage, image display, and data communications. The system will reduce the amount of time required to obtain images for clinical review, and also facilitate research by making population and cross-modality studies more feasible. During FY83 a study of the available technology has been conducted, and an expandable system architecture has been proposed.

Automated Management of Critically Ill Patients (CC). This research project is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal of the project is to use computer-based instrumentation to aid in the differential diagnosis of disease states and the implementation of therapeutic modalities through automated technology. A state variable approach is used in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Empirical clinical data and realtime monitored values are utilized in model validation. Several alternative methods for closed-loop automated medical interventions are being investigated.

Computer Interfaces for Clinical Laboratory Instruments (CC). Microprocessor-based interfaces, developed by CSL, were first used in the Clinical Pathology Department (CC) to link two Coulter automated cell counters to the Clinical Pathology Laboratory Computer. This was followed in February 1982 with the development of a computer-assisted hematology morphology data handling system. That system was quickly used to capacity. This year we are installing a similar system to extend the capabilities of the present system. A total of eight user stations will be provided for online white cell differential counting.

Automated Pulmonary Physiology Testing (NHLBI). This project was brought to a successful completion by mid-year. Fully automated lung static compliance and inspiratory muscle strength procedures are now routinely performed in the Pulmonary Branch's pulmonary physiology/exercise laboratory. Under the control of a MINC 11/03 computer system, data is acquired and analyzed in realtime, with graphical and textual reports produced at the completion of each procedure. Steady state treadmill exercise testing has been partially automated. Although data are manually

entered, analysis and report generation are fully computerized. Due to a change in clinical priorities, work in progress to enable automatic realtime acquisition of exercise data with breath-by-breath analysis was curtailed. System operations support continued throughout the year.

Pulmonary Branch Support (NHLBI). This project involves assisting the Pulmonary Branch to meet its computer and data processing needs. CSL has continued to help maintain the computer portion of the two Collins automated pulmonary function analyzers. Consultation was provided to help the Pulmonary Branch more effectively use the NIH Central Computer Facility for office and scientific applications.

Anesthesia Computer System (CC). This project is a collaborative effort between CSL and the Anesthesiology Service, CC to evaluate improved instrumentation techniques and to identify and investigate ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring and automated recordkeeping in the operating room and on a greater use of noninvasive monitoring methods. This year work continued on the development of plans to guide future work. An investigation was begun of the potential usefulness of a mass spectrometer gas analyzer in the operating room to monitor inhaled and exhaled gas concentrations. Various technologies are being explored to develop a monitoring and reporting system for the operating room.

Medical Information Technology Project. This project is concerned with the development of better ways to automate the essential physician contribution to the health care record. For a second year, in collaboration with two practicing dermatologists, we are field testing an ambulatory patient care treatment system. It is designed to help the physician generate patient information and treatment schedules, pharmacy prescriptions, medical and surgical reports, laboratory test requests and results, and referral letters to other doctors. Physicians interact with the system using high speed user-friendly menu selections with many default fields preselected. Because most of the clinical software is table driven on a microcomputer, it can be

adapted to other clinical care and research environments.

Laboratory Investigation

Molecular Graphics and Sequence Analysis

(NIADDK, NCI, NIDR). The sequence of some regular proteins, together with other structural information such as data from x-ray diffraction, fiber diffraction, electron microscopy, and spectroscopic analysis can be used to evaluate models of the protein structure. Four projects have been using modeling techniques developed at NIH and sequence analysis to better understand the protein structure. We have recently published a new interpretation of the x-ray diffraction data for collagen fibrils. Cyanogen bromide fragments of keratin filaments are being studied to understand their structure and to compare keratin with other filamentous proteins. Analysis of myosin and streptococcal M proteins is continuing as sequences become available.

Electron Microanalysis Facility (DRS). CSL is collaborating with BEIB, DRS to develop an automated electron microanalysis facility consisting of two electron microscopes interfaced to a PDP-11/60 computer system. The facility is being used for research into the elemental composition of biological specimens and for the development of new techniques in electron microscopy. CSL designed and implemented the computer system, which acquires and displays the spectra and images resulting from Electron Energy Loss (EEL) and x-ray spectrometry. This year, both EEL and EDS imaging became operational and are in routine use on many biological research projects. The EEL images are the first successfully produced on a STEM and the first to be properly compensated for mass thickness effects. The second electron microscope, a Cameca electron microprobe, was interfaced to the computer and implemented using existing data acquisition and imaging software. Data processing and image display capabilities of the system were greatly enhanced.

Molecular Interactions Laboratory Data System (NHLBI). This microcomputer (PDP-03) data system supervises the acquisition and processing of

information from an analytical ultracentrifuge and a circular dichroic spectropolarimeter used in MDB, NHLBI to investigate the interactions between human lipoprotein subunits. Preprocessed data are transferred to the DECsystem-10 for further analysis under MLAB using predefined procedures invoked by a few simple commands. Additions to the system this year include a four-pen digital plotter and the MLAB procedures for plotting both ultracentrifuge and circular dichroism data.

Californium-252 Plasma Desorption Mass Spectrometer Data System (NHLBI). This instrument provides NIH the capabilities of mass analysis for compounds difficult or impossible to analyze by other mass spectrometric means. It also extends the range of mass analysis to compounds with molecular weights in excess of 5000. Hardware enhancements made in the system this year include the addition of a line printer, another 256K bytes of memory (total of 768K bytes), and an additional direct memory access channel controller to be dedicated to the mass spectrometer interface.

Distributed Laboratory Data Acquisition and Control System (DLACS) (NIADDK). A Distributed Laboratory Data Acquisition and Control System (DLACS) has been implemented for NIADDK. The new system consists of a network of remote microcomputers connected in a star configuration through a communications processor to a central processing computer. The remote microcomputers handle all of the realtime data acquisition requirements and provide instrument control functions when required. The collected data is normalized, buffered, and transmitted as files over a serial line, using a standard block protocol, to the communications processor. The communications processor serves as a store and forward front end for the central computer. Currently there are eight satellites connected to the system supporting eleven instruments. Processing software provided at the host allows DLACS data files to be: added, subtracted, averaged, smoothed, baseline corrected, integrated, differentiated, multiplied by a constant, and added to a constant. The results may be displayed graphically on a Tektronix terminal, typed at a terminal, printed on the line printer, or plotted on an X-

Y plotter or transmitted to the NIH DECsystem-10 for additional processing.

Personal Computers in Laboratory Application (DCRT). Personal computers have become a viable alternative to assembling board-level microcomputer systems for many laboratory applications. They offer a substantial "head start" and form the basis for programmable acquisition and control systems. We are evaluating laboratory interfacing hardware and software so that we can assist users in configuring systems for a variety of laboratory applications.

Program Management And Administration

Small Animal Data Base Management System (DRS). Responses to the Request for Proposals previously developed by CSL for a small animal data management system were received this year. CSL was responsible for the management of the technical evaluation and guided the negotiations with vendors. Technical consultation to monitor the development of the system is being provided and is anticipated to continue over the next few years.

Library Automation (DRS). Since FY79, CSL has been involved in the automation of the NIH Library. This effort has included a requirement study, a survey of the available options, and a cost benefit analysis, and has culminated in a recommendation to purchase a commercially available turnkey library system. Subsequent to system selection, CSL has continued to support the Library by providing technical assistance during the procurement process. During FY83, CSL has been involved in supervising site preparation and system installation, using the NIH Central Computer Utility to develop software needed to edit the Library's bibliographic data base, providing technical support to the contractor hired to edit the data base, and training and otherwise preparing library staff for the introduction of the sophisticated computer-based system.

Biomedical Communications And Conference Support

Computers in Cardiology Conference. CSL continued its support of the annual International Conference on Computers in Cardiology. The Conference provides a forum for direct interaction and exchange between physicians, computer scientists, and engineers who are involved in various aspects of clinical computer systems in the field of cardiology.

Microcomputers in the Laboratory. *Microcomputers in the Laboratory: An Introduction* was the title of an invited lecture presented by CSL staff member Ramon L. Tate at the Training Course on Computers in Endocrinology, May 30 to June 1, 1983, jointly sponsored by the Chair of Endocrinology, University of Sassari, Italy, and the Post Graduate school of Endocrinology, University of Florence, Italy. The course, which was attended by approximately 80 scientists from Europe and the Middle East, was held in Porto Cervo, Sardinia. Dr. Tate also conducted a workshop session that dealt with selecting and implementing a laboratory microcomputer system.

Minority Biomedical Research Support. CSL supported NIH minority biomedical research assistance programs by participating in the NIH Visiting Professor Program and by preparing and presenting a workshop on laboratory computing to the annual MBRS symposium.

CSL Consulting

This year, as in past years, CSL provided consultative assistance to several intramural and extramural program areas.

- CSL helped the Allergenic Products Branch, Bureau of Biologics to implement a laboratory computer system by adapting a data acquisition software package that we previously developed for another project.
- Several CSL staff members served on NCI evaluation and source selection committees for proposed computer support contracts.

- Two activities reported last year as collaborative projects with NHLBI (Potentiometric Titration Controller and Metabolic Energy Measurements) were successfully continued by NHLBI investigators with CSL providing only occasional microcomputer technical consultation.
- The Cardiology Branch, NHLBI, intends to purchase a digital angiographic imaging system for their new cardiac catheterization laboratory. CSL helped to evaluate their requirements and surveyed the market to identify acceptable systems.

Computer Research And Technique Development

Image Processing Facility (DCRT). This project provides a utility to display and analyze digital images. The system consists of a powerful 32-bit computer with a mixture of medium and high resolution video displays. A high resolution microdensitometer allows precise digitization of images acquired from a variety of sources (e.g., electron microscope). The system was installed this year and is in use by a limited number of investigators. Completion of the system is forecast for 1984.

Analytic Models of Computer System Performance (DCRT). This project involves the development of analytic models that can be used to evaluate the performance of computer systems. During the past year, the work on modeling and analyzing computer systems using the graph theoretic model called timed Place-Transition (P-T) Nets was continued. This included the development of new methods for determining net invariants and new models for demonstrating the dynamics of computer systems. Detailed models of computer bus control techniques and the operation of a commercial array processor were constructed. These models were analyzed using a method that was developed for evaluating computer system performance with timed P-T Net models. The development of a state variable P-T Net model of the interconnection of two or more microprocessors was continued. This model provides a framework for determining the avoidance of deadlock and the

maintenance of throughput in multiple microprocessor systems. In FY84, timed P-T Net models will be used to develop more analytic tools for evaluating computer system performance.

Verbal Access to Computers for the Blind (DCRT). Several years ago, CSL developed a voice output terminal that permits the blind to access computers independent of sighted assistance. This year, we assembled and installed one of these terminals for a blind NEI scientist to use in his laboratory. We also are investigating the use of voice output with analytical laboratory instrumentation. Finally, we are developing a voice output attachment for the DCRT-supported personal computer workstation to extend the availability of these systems to blind users.

Medical Image Data Compression (DCRT). This project involves reducing the number of information carrying units used to represent a medical image in order to improve the efficiency of transmission and storage of such images. Various image data compression techniques and their application to medical images are being evaluated with regard to the amount of compression attained and the quality of the reconstructed image. Methods for implementing these techniques that will be suitable to the clinical environment are being developed.

Research Projects

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		Z01 CT00050-04 CSL
PERIOD COVERED		
October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the bar lines.)		
Computer Support to Flow Cytometry/Electronic Cell Sorting (FC/ECS)		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.)		
(Name, title, laboratory, and institute affiliation)		
Ronald Pico, Electronics Engineer, CSL, DCRT		
COOPERATING UNITS (if any)		
CSL, DCRT; R.J. Romanoff, Computer Specialist; L.K. Barden, Electronics Engineer; L. Freeman, Computer Programmer; W. Gandler, Electronics Engineer. 1, NCI; S.O. Sharrow, Chemist; D.A. Stephany, Biologist.		
LAB/BRANCH		
Computer Systems Laboratory		
SECTION		
Processor Design Section		
INSTITUTE AND LOCATION		
DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.5	4.5	

Computer Support for Flow Cytometry/Electronic Cell Sorting (FC/ECS)

This project provides PDP-11 computer support at various levels for four Becton-Dickinson FACS II and one Coulter MDADS FC/ECS instruments. Data acquisition is via an NIH-designed interface to the computer. Data display and analysis for high sample throughput is the principal system feature. Currently, there are two versions of data acquisition and analysis systems developed and supported by CSL for the Cell Sorter Community at NIH. One version uses a single computer that runs under the RT-11 operating system. Another version, referred to as the RSX system, uses at least two computers. A host computer, a Digital Equipment Corporation (DEC) 11/24 is used to analyze and store data. Satellite computers, one (LSI-11/23) per instrument, are used for data acquisition and are connected to the host through a high-speed direct memory access (DMA) link. The RSX system offers multiuser and multitasking support, improved recordkeeping facilities, and enhancements for data acquisition and data analysis. An RSX system was installed at I, NCI, during the fourth quarter of FY83.

Background and Objectives: Since FY75 CSL has provided engineering, system integration, and software support necessary to meet the data acquisition, data display, and analysis needs of several investigators using FC/ECS instruments at NIH. Software development and testing is done on a DEC PDP-11/24 computer system owned by CSL. This allows investigators to have full use of their systems while new software is being developed.

Both the RT-11 and RSX systems allow data collection of up to four parameters on individual cells. Typically these are light scatter, two frequencies of fluorescence, and cell volume. The data can be collected in single parameter or correlated dual parameter modes. Data analysis and display programs allow the experimenter to produce various statistics and hardcopy displays from the acquired data. The displays include three-dimensional pictures, contour maps, and vertical slice sections.

Progress in FY83: The major effort in FY83 was continuing the development of the RSX-11M system. The RSX system was developed for I, NCI in order to provide more effective support of current and anticipated workloads and more sophisticated data acquisition and recordkeeping functions. This system is available to other NIH FC/ECS sites as required.

It was decided in FY81 to replace the DEC VT-11 graphics display device with a Tektronix 4025 and to support this terminal on the RSX system. A contract was negotiated with Electronic Data Systems, Inc., to assist CSL personnel in developing software packages for displaying graphs on the T4025 or any terminal that is driven by Tektronix 4010 graphic commands. All four of the major FC/ECS data display and analysis programs were rewritten to run under RSX-11M, using the new graphics software package. Several improvements to these display and analysis programs were made in FY83 in order to improve their use.

A tape-to-disk transfer (TDXFER) program, written and tested in FY83, processes raw list mode data on tape into a matrix (PHA) form and stores this matrix on disk. A user can preview list mode data on the T4025 graphics terminal, in order to determine parameter values necessary to process the data into matrix form. The program is designed to automate multiple processing loops, each with differing parameters, so users need not interact during what may be a lengthy period of time.

The new data acquisition system environment consists of a PDP-11 host computer running RSX-11M and up to eight LSI-11 based satellites, each running RT-11, connected to the host via an interprocessor link.

Data acquired by a satellite is sent over the link and stored at the host site. The satellite link software is common to all satellites, but distinct from the host link software. Together, the host and satellite link software provides file transfer capability.

The development of the link software was completed in FY82 and the hardware for a complete satellite system was acquired. The acquisition hardware and software of the LSI-11 system was tested in the second quarter of FY83. The RSX satellite is designed to collect up to

four single parameters simultaneously with one correlated dual parameter pair, or it can collect up to two simultaneous correlated dual parameter pairs.

An important feature of the satellite system is the ability to create a "laboratory notebook" as a permanent hardcopy rather than continuing this as a manual task as in the RT-11 systems. This "notebook" concept is an integral part of the software that provides interaction with the operator via a DEC VT-100 terminal. Errors are reported in detail on the terminal screen.

The CSL development system was updated with a 11/24 processor in the second quarter of FY83. CSL has also responded to many external requests and has provided copies of the interface hardware schematics, software, and documentation to FC/ECS sites in the U.S., Australia, and Europe.

Proposed Course: In the forthcoming year, CSL plans to continue development on the RSX system by adding features that will take advantage of the data management capability designed into the system. In addition, new capabilities will be added to the data analysis software and some effort is expected to be spent on automating analysis, and/or acquisition software so that many steps can be performed without operator intervention. If resources permit, the RT-11 analysis programs will be expanded to include Cell Cycle Analysis and several other high priority requirements. CSL will also continue to maintain existing RT-11 based FC/ECS sites at NIH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		201 (LINDS) - Gw. CSL
PERIOD COVERED: 1982 to September 30, 1983		
TITLE OF PROJECT: Cardiac Scintillation Probe		
PRINCIPAL INVESTIGATOR (Last name, first name, middle initial, degree, title, and affiliation)		
Harold G. Matkov, Electronics Engineer, CSL, DART		
NM, CC: S. Bacharach, Physicist, M. Green, Physicist, J.B. Kober, P. Berman, Cardiologist, D. Rosen, Cardiologist.		
LAB BRANCH		
Computer Systems Laboratory		
Section		
Programmer Design Section		
INSTITUTE AND LOCATION		
DART, NIH, Bethesda, Maryland 20205		
TOTAL MANPOWER		
0.25	0.25	Other

Cardiac Scintillation Probe

CSL has continued the development of its Cardiac Scintillation Probe System begun in 1977. This nonimaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. By simultaneously measuring LV volume and LV pressure, parameters such as LV compliance can be continuously monitored, in addition to such measurements as ejection fraction, filling and ejection rates, and temporal relationships. This year the probe continued to be used to study the effects of nifedipine and verapamil on patients with coronary artery disease.

The probe is also being used to monitor the left ventricle performance of patients in the Medical Intensive Care Unit. The pressure-volume relationships produced by the probe system allowed the effects of drugs to be quantitated in a manner not possible before. Development is continuing on increasing the detection efficiency of the probe and in quantifying the limitation of the technique. The cardiac scintillation probe is a transportable device used to noninvasively monitor left ventricular function. The system uses Nuclear Medicine ECG-gated scintigraphic techniques and consists of a small detector and microcomputer system mounted on a cart.

Background and Objectives: The development of the cardiac scintillation probe is a continuation of CSL's collaboration with the Nuclear Medicine Department, CC, and the Cardiology Branch, NHLBI. Originally this collaboration resulted in the development of a noninvasive cardiac imaging technique known as ECG-gated scintigraphic angiography using a scintillation camera. However, if the images are not required, then a time-activity curve of the left ventricle could be generated by a much smaller and simpler system. In 1977 CSL began the development of a cardiac scintillation probe system, using a small NaI detector and microcomputer system. This system produces a time activity curve (LV volume curve) that can be used to calculate various parameters of cardiac function such as ejection fraction, peak ejection rate, peak filling rate, and their temporal relationships. The system is easily transportable and allows continuous monitoring of cardiac function at the bedside or other location in

the Clinical Center outside the Nuclear Medicine Department.

Methods: The system consists of a three-inch diameter NaI scintillation probe, probe electronics, microcomputer system, and display. The system is programmed to acquire scintillation data from the probe, to process the data, and to plot and display various parameters of left ventricular (LV) function. This nonimaging, ECG-gated probe, when used in conjunction with ventricular catheterization, permits simultaneous quantification of the variation of LV volume and LV pressure. Parameters such as LV compliance can be continuously monitored. In the catheterization laboratory, pressure-volume measurements are used to study the effects of drugs on patients with various heart diseases.

Progress in FY83: This year the probe continued to be used in the catheterization laboratory to study the effects of nifedipine and verapamil on patients with coronary artery disease. The data acquisition and some of the processing is now being performed by the Nuclear Medicine Department. A Hewlett-Packard computer system has been ordered to replace the Intel microcomputer system used for the probe. The Hewlett-Packard computer will accommodate new requirements for the probe system and be compatible with the existing analysis software available in the Nuclear Medicine Department.

The application of the probe in the Medical Intensive Care Unit, CC is continuing to be investigated. The probe would be used to continuously monitor left ventricular function at the bedside.

Significance to Biomedical Research: Nuclear Medicine techniques provide a relatively noninvasive procedure to assess left ventricular function. The cardiac scintillation probe permits this capability to be used for clinical research studies at the bedside and in the catheterization laboratory. The pressure volume relationship produced by the probe system allows the effects of drugs to be quantitated in a manner not before possible.

Proposed Course: Development activities in response to new applications are expected to continue. CSL will

investigate making the probe and camera systems compatible. Making the system compatible to the extent possible will reduce the resources required to support the probe system and will allow new capabilities developed for the camera systems to be implemented quickly on the probe system.

Publications:

- Bonow, R., Ostrow, H., Rosing, D., Cannon, R., Allen, S., Maron, B., Bacharach, S., Green, M., and Epstein, S.: Verapamil Effects on Left Ventricular Pressure-Volume Analysis with a Nonimaging Scintillation Probe. *Circulation* (in press).
- Green, M., Ostrow, H., Bacharach, S., Allen, S., Bonow, R., and Johnston, G.: Realtime Scintillation Probe Measurement of Left Ventricular Function. *Nuklear Medizin* 20: 116-123, 1981.

resolution x-ray system with digital subtraction angiography capability.

Of primary interest is the utilization of the Medical Intensive Care Unit's computer systems in the study of the etiology and therapy of septic shock.

Background and Objectives: The Medical Intensive Care Unit (MICU), which is administered by the Department of Critical Care Medicine in the NIH Clinical Center, receives critically ill patients from clinical programs of NIH. The MICU comprises a five-bed ward area, a pair of isolation beds, and a vascular research laboratory. The research goals of this unit include the development of techniques for automated patient monitoring and noninvasive measurements of the cardiovascular and respiratory systems. In addition, catheterization studies are performed as necessary to obtain data that are available only through invasive methodology.

Working with Clinical Center staff, CSL contributed to the engineering design of the intensive care unit. CSL also undertook the specification, procurement, and installation of the bedside patient monitoring equipment and the six computer systems:

1. a Patient Data Management System used for automatically monitoring patient variables, manually entering patient data, retrieving information online, and keeping medical records;
2. a Vascular Research Subsystem used for acquiring and processing cardiovascular pressure waveforms, measuring cardiac output, displaying measured results online, and generating a cardiac catheterization report;
3. a Software Development Subsystem used for developing software for the above described systems;
4. an Ultrasound Imaging Subsystem used to allow the visualization of intracardiac structures via multiformal displays, and facilitate the detection of structural abnormalities and other cardiac defects;
5. a Medical Mass Spectrometer Subsystem used for monitoring both the patient airway gases and the gases delivered by the patient's respirator at all seven MICU beds; and

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00054-04 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (do not exceed 100 characters) (This must fit on one line between the brackets) Medical Intensive Care Unit Patient Monitoring Computer System		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Kenneth H. Kemper, Electronics Engineer, CSL, DCRT		
COOPERATING UNITS (if any) CCMD, CC: J.E. Parrillo, M.D., Chief, Critical Care Medicine; S.L. Huntley, Supv. Critical Care Technician. CSL, DCRT: L.K. Freeman, Computer Programmer; J.M. DeLeo, Computer Systems Analyst. BEIB, DR5: J.F. Fessler, Engineering Technician.		
LABORATORY Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS 0.8	PROFESSIONAL 0.8	OTHER

Medical Intensive Care Unit Patient Monitoring Computer System

The dynamic events occurring within the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system. Capabilities of the system include online data acquisition and analysis, medical recordkeeping, tabular and graphical data displays, and feedback control, as required in support of patient care and research protocols. Elements include a minicomputer-based Patient Data Management Subsystem, a Software Development Subsystem, and a Medical Mass Spectrometer Subsystem.

The facility also contains a state-of-the-art catheterization laboratory that includes a flexible computerized Vascular Research Subsystem, with physiologic waveform processing features, and a high

6. a Pulmonary Function Testing Subsystem used to calculate parameters such as vital capacity and lung volumes, and to generate flow-volume loops.

The first four systems were purchased from the Hewlett-Packard Corporation and all use identical minicomputers. The Chemetron Corporation manufacturers the microcomputer-based mass spectrometer system. The Collins Corporation designed and manufactured the microcomputer-controlled Pulmonary Function Testing Subsystem.

Major Findings: The automation of the MICU has aided the medical staff by managing the large amount of data needed for the care of the critically ill patient, performing desired calculations, and allowing measurements that would not otherwise be possible.

Progress in FY83: Modifications were made to the main Vascular Research Subsystem and the mobile noncomputerized Vascular Research subsystem, in order to improve their data collection capabilities and ease of operation.

The ultrasound imaging subsystem was upgraded to improve image resolution by doubling the number of receiving crystals in the phased array transducer.

A Cardiac Probe, developed jointly by CSL staff and the Clinical Center's Nuclear Medicine Department, was interfaced to the Software Development Subsystem. This device provides left ventricular volume data by counting gamma ray-induced scintillations, after the administration of injectable radioisotopes. Software was developed to produce Beat Length Histograms and Joint Interval Histograms from the scintillation data, as well as single cycle and averaged left ventricular volume curves.

Proposed Course: Future efforts will center on hardware and software modifications necessary to enhance the system's ability to support patient care and research protocols. Possible modifications to the primary Patient Data Management Subsystem include the addition of urine output measurement scales and the computerization of fluid infusion therapy utilizing existing microprocessor-controlled infusion pumps.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00084-03 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. This must fit on one line between the borders.) Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) James M. DeLeo, Computer Systems Analyst CSI, DCRT		
COOPERATING UNITS (if any) LB, C: Floyd Taub, Research Associate; Brad Thompson, Section Chief.		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIN, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.1	PROFESSIONAL 0.1	OTHER

Computer Analysis of Autoradiographic Images of Recombinant DNA Colonies

A computerized methodology for analyzing autoradiographic spot images associated with recombinant DNA bacterial colonies was developed in collaboration with scientists in NCI. This system represents a unique refinement in a method to directly identify cloned sequences complementary to messenger RNA that are developmentally or hormonally induced.

Spot density measurements are computed from digitized images produced via microdensitometry. These measurements are corrected for variability in exposure and local background, calibrated to hybridization standards, and normalized for comparison purposes. The system provides a variety of graphical and tabular output that effectively summarizes experimental results and identifies significant induced hybridization events.

Background and Objectives: NCI scientists have been refining techniques to directly identify cloned DNA sequences complementary to messenger RNA that are developmentally or hormonally regulated. This refinement has led to a methodology that produces autoradiographic spot images representative of the amount of hybridization. The objective of this project is to provide an automated procedure for a quantitative analysis of understanding these images.

Methods Employed: Cloned bacteria are grown on agar in microtiter wells, transferred to filter paper, and hybridized to end-labeled mRNA or cDNA probes. Autoradiographs of the filters are digitized and the density of each spot relative to background is established by means of CSL-developed image processing software operational on the DCRT Evans and Sutherland PDP-11/70 computer system. Compensation for variations in background, film exposure conditions, and hybridization are included in the methodology. A variety of graphical output including scatter diagrams, histograms, and listings is provided.

Progress in FY83: A paper has been written that describes the use of this system in analyzing the in vivo response of rat liver to glucocorticoids, as well as the application to other biological systems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		201 CT00086-02 CSL
PERIOD COVERED		
October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the brackets)		
Computer Assisted Tomography (CAT) Scan Image Analysis in Aging Studies		
PRINCIPAL INVESTIGATOR (Last name professional personnel on subsequent pages)		
(Name, title, laboratory, and institute affiliation)		
James M. DeLeo, Computer Systems Analyst, CSL, DCRT		
COOPERATING UNITS (if any)		
LN, NIA; M. Schwartz, Medical Staff Fellow; S.I. Rappaport, Chief.		
LAB BRANCH		
Computer Systems Laboratory		
SECTION		
Systems Design Section		
INSTITUTE AND LOCATION		
DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS	PROFESSIONAL	OTHER
0.2	0.2	

Computer Assisted Tomography (CAT) Scan Image Analysis in Aging Studies

An interactive image analysis computer procedure to measure various parameters from Computer Assisted Tomography (CAT) scans of the human brain was designed and implemented on the DCRT Image Processing Facility. This procedure was used to measure and analyze various morphological features of the brains of normal volunteers representing a wide age span as well as adults with autism, Alzheimer's Disease, and Down's Syndrome. Results were reported at two professional meetings. Technical papers describing this work are in preparation. Efforts to transport this methodology to a newly installed NIH

computer system have begun and are reported separately.

Background and Objectives: The purpose of this project is to study changes in the human brain structure during normal aging and during brain disease processes associated with aging by means of measurements made from Computer Assisted Tomography (CAT) scans of human brains.

Methods Employed: CAT scans are transported to the DCRT Image Processing Facility via magnetic tape. Through interactive analysis of the CAT scan images, an investigation is able to obtain a wide variety of descriptive measurements such as sizes and attenuation values of brain substructures, and percent composition of the intracranial space in terms of white matter, gray matter, and cerebral spinal fluid.

Progress in FY83: Several brain CAT scans of normal volunteers were processed. Results supporting the theses of ventricle enlargement and gray matter reduction in normal aging were presented at meetings of the American Academy of Neurology and the American Psychiatry Association. Papers describing these findings and the methodology have been written. Efforts to transport the methodology to a newly installed NIA computer system have begun. The need for beam hardening and skull/brain partial voluming corrections in brain composition estimation was found to be necessary.

Significance to Biomedical Research: This quantification methodology will greatly augment visual interpretation of brain CAT scans. It may provide a deeper understanding of brain structure associated with normal aging and disease processes. It is also possible that this work will produce new diagnostic tools.

During the course of this work it was discovered that brain composition estimates were significantly biased by radial and apical beam hardening artifacts and skull/brain partial volume effects. Empirical corrections for these effects are essential for improving upon these estimates.

Proposed Course: Future plans include submitting technical papers for publication and completing the

transfer of the methodology to the NIA computer system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00087-02 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Robust Boundary Detection of Necturus Gall Bladder Cells		
PRINCIPAL INVESTIGATOR (Last name of professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) James M. DeLeo, Computer Systems Analyst, CSL, DCRT		
COOPERATING UNITS (if any) LKEM, NHLBI: K. Spring, Research Physiologist; P. Jensen, M.D., Guest Worker.		
LABORATORY Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS 0.4	PROFESSIONAL 0.4	OTHER

Robust Boundary Detection of Necturus Gall Bladder Cells

The boundary detection algorithm previously described has been implemented, tested, and refined on the DCRT Evans and Sutherland Image Processing Facility. This algorithm performs automated planimetry on light microscopy video images of optically microtomed sections of in vivo Necturus gall bladder cells to provide time histories of cell volume changes. The refined algorithm searches extrema of pixel variances along pin filters orthogonal to guided segments of radial spokes emanating from the cell section centers. Efforts to transport this algorithm to an NHLBI computer system for continuing laboratory use have begun.

Background and Objectives: Epithelial cells of Necturus gall bladder regulate their volume after a change in osmolality of their bathing solution. The Laboratory of Kidney and Electrolyte Metabolism has developed a computerized methodology for time-tracking cell volume changes through interactive planimetry of video images of cells visualized in a light microscope. The Computer Systems Laboratory was requested to develop a specialized robust cell boundary detection algorithm to enhance overall throughput processing efficiency.

Methods Employed: The refined boundary detection algorithm works as follows:

1. The investigator points to the center of the cell.

2. Parameters associated with locations along segments of rays emanating from the center are computed. The number of rays is user specified. Ray segment selection is initially specified and later guided by certified edge points associated with previously processed cell sections. Computed parameters include means and variances and their derivatives of opacity values along pins emanating from each ray segment pixel. The number and length of pins are user specified.

3. Local maxima of an edge point probability function computed from a normalized combination of parameters collected in Step 2 are determined and tagged as candidate edge points.

4. Candidate edge points are screened and pruned for redundancy and for being out of range.

5. Missing edge points are searched for over narrower ray segments as guided by certified known neighboring edge points.

6. The final list of edge points is smoothed, connected, and integrated to give area.

7. Steps 1 to 6 are repeated over all cell segments to obtain cell volume.

Progress in FY83: A new set of test images were brought over to the DCRT Image Processing System. A variety of smoothing and filtering techniques were tested leading to the selection of the described pin filtering technique. Hardware and software work has begun to make the algorithm operational in the NHLBI research laboratory environment.

Significance to Biomedical Research: Application of quantitative light microscopic techniques to study cell volume changes due to fluid and ion transport in living epithelial tissues has already proven to be a powerful and effective research tool. An accurate, efficient, robust cell boundary detector algorithm would greatly improve upon the utility efficiency and throughput speed of this methodology.

Proposed Course: Testing and refining of the algorithm will continue. Implementation of the algorithm for production use in the LKEM/NHLBI research laboratory environment is planned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00081-03 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the brackets) Rehabilitation Medicine Department Computer System		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Robert L. Martino, Electronic Engineer, CSL, DCRT		
COOPERATING UNITS (if any) RM, CC, W.O. Jarrett, Expert, Biomechanical Engineering; G.C. Hunt, Physical Therapy Research Coordinator; W. Schneiderwind, Chief, Physical Therapy Service; N.L. Gerber, Chief, Rehabilitation Medicine Department.		
LAB BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.6	PROFESSIONAL 0.6	OTHER

Rehabilitation Medicine Department Computer System

This project involves the development of computer techniques in collaboration with the Department of Rehabilitation Medicine of the NIH Clinical Center. CSL has recommended computer techniques that can be used to automatically acquire anatomical and physiological information from patients, to perform the required calculations on the data obtained, and to display the necessary results to the medical staff. The automated techniques include the measurement of body forces (hand and ground reaction forces), electromyograms (electrical activity of the muscles), and body kinematics (the position and angles of the limbs and joints in space and time). An Automated Biomechanics Laboratory System that provides these measurements was purchased in FY83. The computer part of the system will allow the medical staff to enter patient and staff data into a data base with computer generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data. In FY83, the physical space for the purchased system was designed and the system was installed. The Automated Biomechanics Laboratory will begin operation at the start of FY84.

Background and Objectives: The Department of Rehabilitation Medicine provides psychiatric evaluation and treatment, physical therapy, occupational therapy, and speech therapy for NIH Clinical Center patients referred by Institute physicians. In addition, it develops various indices to evaluate these services. This

department supports the efforts of, and collaborates with, Institute physicians engaged in research relevant to physical rehabilitation medicine. It also initiates both clinical and basic research independent of the Institutes in the rehabilitation of mentally and physically handicapped individuals.

In support of these goals, CSL is developing a computer system. Initially, the department will use the system for the following three projects:

1. The Automated Biomechanics Laboratory: a laboratory that will be used to automatically measure the position of the limb segments in space, the patient ground reaction forces, and the electromyographic signals from the muscles in the limbs;
2. The Hand Dynamometer Instrument: a device that will be used to measure the magnitude and direction of the forces in the hand and to develop clinical tests to diagnose the mechanical and functional status of the hand, arm, and shoulder;
3. The Physical Therapy Quality Assurance System: a data base system that will be used to assess medical staff effectiveness in providing the types of patient care needed, determine staff workload and scheduling, and identify areas for clinical research for the Physical Therapy Service.

Progress in FY83: During the past year, an Automated Biomechanics Laboratory System was purchased from Oxford Medilog, Inc. The instrumentation that was purchased included five motion cameras with infrared light sources that are used to acquire the spatial coordinates of anatomical points on the patient's body with reflective markers, two force platforms that are used to measure patient ground reaction forces, and hard wired electromyogram acquisition hardware that is to measure patient muscle activity. This instrumentation is connected to a Digital Equipment Corporation VAX-11/750 computer system that performs the necessary data acquisition, calibration, processing, display, and storage functions. The equipment was installed at the Department's new Clinical Center location in an area that was designed to accommodate the specialized instrumentation and computer system.

Development of the Physical Therapy Quality Assurance Data Base System was continued on a small computer system. It will be transferred to the computer that was purchased with the biomechanics laboratory system. The Biomedical Engineering and Instrumentation Branch of NIH's Division of Research Services continued development of the hand dynamometer instrument.

Also, during the past year, the collaboration with the Gait Analysis Laboratory, Department of Orthopedic Surgery, Children's Hospital Medical Center, and Harvard Medical School was continued. In the future, computer programs, patient data, and engineering and medical expertise will be exchanged with this group.

Significance to Biomedical Research: The computer system will be used with arthritic, orthopedic, and neurological patients, and with amputees in order to evaluate drug therapy, orthotic and prosthetic devices, and medical interventions. It will also be used as a teaching tool to help these patients learn to function with their disability in an efficient manner. Many medical centers in the United States, Great Britain, Europe, and Japan are presently establishing automated biomechanics and gait analysis laboratories. Therefore, any new developments made on this project will benefit users of these automated systems, as well as patient care and clinical research within the Department of Rehabilitation Medicine at NIH.

Proposed Course: During the coming year, the Automated Biomechanics Laboratory System will be placed in clinical operation. Initially, the mechanics of motion of amputees and the impact of prosthetic design on gait characteristics will be evaluated. Also, the effects bracing may have for contiguous joints of the upper and lower extremities in arthritics will be studied.

Many additions will be made to the system in the future including improvement of the EMG acquisition hardware; selection and integration of visual cameras and video recorders, including the electronics needed for synchronization with the motion cameras; implementation of energy expenditure calculation software; and the development of methods for accurately determining the velocity and acceleration of

anatomical points from acquired motion data including consideration of the required camera resolution and frame rate, and digital differentiation techniques.

Publications:

Martino, R. L., and Gerber, L. H.: An Automated Biomechanics Laboratory Applied to Rehabilitation. *Proceedings of the Fifth Annual Conference of the IEEE Engineering in Medicine and Biology Society* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		Z01 CT00109-01 CSL
PERIOD COVERED		
October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)		
Aging Studies Image Analysis System		
PRINCIPAL INVESTIGATOR (for other professional personnel on subsequent pages.)		
(Name, title, laboratory, and institute affiliation)		
Hal A. Fredrickson, Computer Systems Analyst, CSL, DCRT		
COOPERATING UNITS (if any)		
CSL, DCRT: J.M. DeLeo, Computer Systems Analyst; W.L. Kiso, Electronics Engineer. LN, NIA: M. Schwartz, Medical Staff Fellow; N. Cressy, Visiting Associate; S.I. Rapoport, Chief.		
LABORATORY		
Computer Systems Laboratory		
SECTION		
Systems Design Section		
INSTITUTE AND LOCATION		
DCRT, NIA, Bethesda, Maryland 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.8	0.8	

Aging Studies Image Analysis System

The Computer Assisted Tomography (CAT) image analysis task performed on the DCRT Evans and Sutherland PDP-11/70 computer system and reported as Project Z01 CT-00086-02 CSL has been transferred to a PDP-11/34 computer in the National Institute on Aging. The 11/34 computer is equipped with a DeAnza IP6400 image display system with a 512 x 512 24-bit pixel resolution. This allows the Positron Emission Tomography (PET) scan images and the CAT images to be analyzed on the same system with the eventual goal of correlating PET and CAT scans.

Background and Objectives: To provide the Laboratory of Neurosciences, NIA, an image processing facility that will be used to measure changes in the human brain determined by CAT and PET scans.

Methods Employed: CAT scans are obtained by computer disk from the DCRT Evans and Sutherland System (future CAT scans will be obtained by tape from Diagnostic Radiology). PET scans are obtained by disk from Diagnostic Radiology. The PET or CAT images are then displayed on a DeAnza color monitor for analysis. The PET image analysis software is a modification of a

package provided by NIMH. CAT analysis is based on work developed for the DCRT Evans and Sutherland (E&S) System by CSL.

Progress in FY83: The ability to display CAT image data originally created using the DCRT E&S System has been provided on the PDP-11/34 DeAnza configuration. Percentages and areas of CSF, white matter and gray matter are determined.

Proposed Course: Provide the ability to work with PET and CAT scans simultaneously. Also, to develop the capability of outlining a region on the CAT image and then determining the homologous region on the PET image.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00100-02 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (40 characters or less. Title must fit on one line between the bar lines) Positron Emission Tomography (PET) Facility		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Arthur J. Fishman, Computer Specialist, CSL, DCRT		
COOPERATING UNITS (if any) CSL, DCRT; W.L. Risso, Electronics Engineer, NM, CC: R.M. Kessler, M.D., Head, Positron Emission Tomography Section.		
LAB BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN YEARS 0.1	PROFESSIONAL 0.1	OTHER

Positron Emission Tomography (PET) Facility

The PET facility of the Nuclear Medicine Department is used to collect and analyze images of the human brain for diagnosis and scientific research. The facility includes a PET Scanner that receives data consisting of gamma emissions from patients and a minicomputer system that operates the scanner, reconstructs the data into cross-sectional slices, and performs other analysis. The facility also includes an offline minicomputer system having an image array processor and color display that is used to interactively perform numerous image enhancement and analysis functions. Various NIH Institutes use this facility to research the aging process, schizophrenia, epilepsy, and other brain functions and disorders.

Background and Objectives: In late FY81, the Nuclear Medicine Department requested assistance in

improving their PET computer facility. At that time, the PET facility was receiving increased usage by various Institutes and had recently lost some of its technical staff. The goal of the project was to improve the existing system's hardware and software, to establish guidelines for collection and storing patient data, and to provide an image analysis system that could be readily operational.

Progress in FY83: There was further development in programming the offline image system to automate procedures for researchers to quickly and efficiently analyze many patient scans. A microcomputer was purchased and programmed to interface a scintillation counter with the offline computer and programs were written to quantize radio isotope activity in patient plasma samples. The PET scanner computer was programmed to include a new disc drive and other peripherals to handle increased data flow.

Proposed Course: There will be an increasing demand for PET scan analysis with the addition of new PET scanners and new protocols. However, due to shortage of staff, CSL has curtailed activity with the PET section and hopes to resume collaboration in approximately one year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00100-01 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (40 characters or less. Title must fit on one line between the bar lines) Picture Archiving and Communication System		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Howard W. Sabrin, Ph.D., Staff Fellow, CSL, DCRT		
COOPERATING UNITS (if any) CSL, DCRT: D. Syed, Chief, Systems Design Section. DR, CC: D.W. Rutz, M.D., Staff Radiologist.		
LAB BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN YEARS 1.2	PROFESSIONAL 1.2	OTHER

Picture Archiving and Communication System

This project encompasses the development of a picture archiving and communications system (PACS) to automate the storage and transmission of medical images at the Clinical Center. Although centered around the Diagnostic Radiology Department, the

system is being designed with the long term goal of serving other imaging-oriented departments, including Nuclear Medicine and Radiation Oncology. The system will consist of state of the art mass storage devices, which will be able to keep several week's worth of data available for immediate viewing, as well as the most advanced network communication, data management, and image display equipment. When in place, the system will allow the storage of images from several modalities in a central facility and will enable physicians to view those images from a variety of locations. A feasibility study is currently being conducted, and procurement is expected to begin in FY84.

Background and Objectives: In addition to the traditional film x-ray, medical imaging today encompasses several new and complex modalities, among them Computed Tomography, Ultrasound, Digital Angiography, Scintillography, Emission Tomography, and others. Some of these modalities are digital in nature, while others produce images in video format. Storage of the images produced by these devices is an arduous and space consuming task, requiring vast film and tape libraries. A physician who wishes to view images generated on more than one of these must do so separately in the viewing areas for each modality, or must obtain hardcopy reproductions of the images. The system under study would enable the physician to view images of all modalities at a single location, either at a console placed in a central viewing area, or at one in his office. Additional viewing consoles could be placed in operating rooms, nursing stations, and conference facilities. The system could allow quick access to images selected by patient, population group, illness, imaging modality, or other factors. A computer security system will prevent unauthorized individuals from gaining access to the image data base.

Progress in FY83: A study of the available technology and of the feasibility of the project has been completed. Many system configurations were considered, and data were collected from the manufacturers of various types of computer, storage, communications, and display equipment. In addition, many consultations were held with personnel from other institutions who are

developing image management systems. A flexible and expandable system architecture has been proposed.

Significance to Biomedical Research: An image management system like the one described above would greatly encourage research by facilitating access to different classes of medical images. A physician wishing to compare images from different modalities, or conduct longitudinal or cross populations studies would be able to view all the images of interest in one session, while sitting at a single viewing station.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00099-02 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (40 characters or less. Title must fit on one line between the borders.) Automated Management of Critically Ill Patients		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Kenneth M. Kempner, Electronics Engineer, CSL, DCR		
COOPERATING UNITS (if any) CCIM, CC: J.S. Farrillo, M.D., Chief, Critical Care Medicine. U. MD: N. DeClaris, Sc.D., Professor, Electrical Engineering Department.		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCR, NID, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.3	PROFESSIONAL 0.3	OTHER:

Automated Management of Critically Ill Patients

This research project is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal is the utilization of computer-based instrumentation to aid in the differential diagnosis of disease states and the implementation of therapeutic modalities through automated technology.

A state variable approach is utilized in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Empirical clinical data and realtime monitored values are utilized in model validation. Several alternative methods for closed-loop automated medical interventions are being investigated.

Background and Objectives: Noninvasive diagnostic and therapeutic techniques generally involve the application of sophisticated electronic technology and mathematical modeling techniques to the detection of pathophysiologic states. Particularly interesting and

important problems involve cardiovascular disorders that give rise to low output syndrome.

There is no singular cause for this syndrome, and therefore effective therapy requires the differential diagnosis of numerous contributory disturbances in cardiovascular homeostasis. Effective therapy principally involves the administration of one or more fluids and/or drugs in a critical care unit environment.

Methods Employed: In order to accomplish the goal of developing systems capable of assisting in the medical management of a critically ill patient on a closed-loop basis, it will be necessary to develop validated models. Calculated physiologic parameters will be compared to measured physiologic data as the patient's response to the selected therapy progresses.

A mathematical formulation of the relevant subsystems will be developed for a patient in a critical care unit setting. This includes the modeling of three principal subsystems: Pharmacokinetics, Drug/Receptor Interactions, and Cardiovascular Dynamics.

Progress in FY83: The mathematical formulations necessary to describe the three major subsystems have been completed. The package of FORTRAN programs that will evaluate the mathematical models are in the final stages of development.

These programs will be implemented on the DCRT Central Facility to simulate the intensive care unit environment, so that automated therapeutic interventions, in response to simulated and actual patient data, may be evaluated with regard to clinical correlation. Program output will include recommendations for therapy as well as predicted pre- and post-intervention physiologic data values.

Significance to Biomedical Research: The use of automated systems in the implementation of therapeutic protocols within a critical care unit adds a new treatment modality and will have a major effect on protocol design. It will afford improvements in protocol design for patient care, clinical drug trials, and the study of the etiology and therapy of specific disease entities. In addition, the automation of therapeutic interventions, as proposed, will significantly expand the clinical and research data bases.

Proposed Course: Existing critical care protocols will be investigated to identify those components in which automated therapeutic modalities can easily be accommodated, within the framework of this research effort. An important aspect to be evaluated is the risk to the patient versus the realizable benefits.

Selected protocols will be implemented utilizing the closed-loop techniques developed in this project, with the objective of carrying out controlled clinical trials and quantitatively evaluating their effectiveness.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		201 CT00098-02 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (If appropriate, list title "Head of the line" and the name of the laboratory) Computer Interfaces for Clinical Laboratory Instruments		
PRINCIPAL INVESTIGATOR (Last name, first name, middle initial, and degree) David C. Songco, Electronics Engineer, CSL, DCRT		
COORDINATING UNIT (if any) CSL, DCRT: V.J. Byrne, Electronics Engineer. CP, CC: J.A. Dunlon, M.D., Ph.D., Staff Physician.		
LAB BRANCH Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MONTHS 0.2	PROFESSIONAL 0.2	OTHER

Computer Interfaces for Clinical Laboratory Instruments

Microcomputers are being applied in the Clinical Pathology Department to extend the capabilities of the Clinical Pathology Laboratory Computer (CPLC) and to automate data acquisition and entry for procedures not previously automated. Two projects have been successfully implemented in this way.

The first involved the linking of two Coulter Model S-Plus automated cell counters with the CPLC. Coulter results now can be certified and released by the technologist within minutes of completion of the analysis. The second project resulted in the development of a Computer-Assisted Hematology Morphology Data Handling System. Each of these projects was characterized by the extensive involvement of the technologists in the human factors design considerations. This collaboration ultimately led to the immediate and enthusiastic acceptance of the systems.

Background and Objectives: After interfacing two Coulter Model-S Plus instruments to the CPLC, the Computer Systems Laboratory and Clinical Pathology Department, CC, developed a Computer-assisted Hematology Morphology Data Handling System. In February 1982, this system replaced the previous method of transcribing manual white cell differential results onto mark sense cards for later entry into the CPLC. Four VT100 CRT terminals are used for direct entry of manual differentials, red cell morphology, and platelet estimates. The terminals are linked to a DEC LSI-11 microcomputer that serves as a controller and also maintains a realtime communication link to the CPLC. With this configuration, Coulter automated cell counting results are retrieved from the CPLC for use by the technologist during the differential counting. When the analysis is complete, the results are transferred online to the CPLC. Based on an average daily workload of 230 analyses, the system has decreased the manpower requirements by 50 percent, changed turnaround time for release of certified results from hours to minutes, and reduced transcription time and errors.

Progress in FY83: The four-station system is being used to capacity. A second system is being installed to accommodate at least four additional stations. This configuration utilizes dual cartridge disk drives in place of the floppy disk drives used in the original system. The faster disk access coupled with the RSX11-M multiuser operating system will allow us to add additional functions and user stations to the system as the need arises.

Proposed Course: The use of microcomputers as programmable interfaces to Clinical Pathology Laboratory instruments, such as the Coulter Model S-Plus, and as interactive data entry and retrieval stations, as with the white cell differential counting system, has been very successful. Plans are underway to extend this technology, possibly by using personal computers, to other instruments and activities within the Clinical Pathology Laboratory.

Publications:

Donlon, J., Wang, L., Lundy, E., Wages, B., Faust, A., and Songco, D.: A Computer Assisted Hematology Morphology Data Handling System. *Proceedings of the Sixth Annual Symposium on Computer Applications in*

Medical Care, Sheraton Washington Hotel, Washington, DC, October 30-November 2, 1982, pp. 270-273.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		Z01 CTD0055-04 CSL
PERIOD COVERED		
October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders.)		
Automated Pulmonary Physiology Testing		
PRINCIPAL INVESTIGATION (List other professional personnel on subsequent pages.)		
(Name, title, laboratory, and institute affiliation)		
Lawrence D. Nadel, Ph.D., Senior Staff Fellow, PDS, CSL, DCRT		
COOPERATING UNITS (if any)		
PB, IR, NHLBI: B.A. Keogh, M.D., Expert. CSL, DCRT: P.S. Flexico, Chief, Project Development Section.		
LAB/BRANCH		
Computer Systems Laboratory		
SECTION		
Project Development Section		
INSTITUTE AND LOCATION		
DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

Automated Pulmonary Physiology Testing

Procedures such as exercise testing of pulmonary compliance and muscle strength are useful in evaluating pulmonary function. By exercising a patient on a treadmill and gradually increasing the workload (i.e., speed and incline), the physician can better assess pulmonary disease, which in its early stages generally does not manifest itself except under physical exertion. To help the physician perform these procedures more effectively, a microcomputer system has been developed to automate realtime data collection and analysis and to display calculations of pulmonary compliance and inspiratory muscle strength.

Steady state treadmill exercise testing has only been partially automated. Although data is manually entered, data analysis and report generation are fully computerized. Work was started to enable automatic realtime acquisition of exercise data with breath-by-breath analysis. However, due to a change in clinical priorities, work was curtailed on the breath-by-breath system. Patient data is stored on a local disk data base for future reference.

Background and Objectives: Physicians monitor pulmonary parameters during exercise to better assess pulmonary function and to diagnose pulmonary dysfunction that only manifests itself under physical exertion. Procedures such as pulmonary compliance

and inspiratory muscle strength also give insight into respiratory function.

Formerly, pulmonary treadmill exercise testing data were processed manually. Data were written down and later entered into a programmable calculator for determination of results. Additional summary statistics and a final report were prepared by hand. Inspiratory muscle strength and pulmonary compliance measurements, done in the same lab, were likewise performed manually. In order to speed both exam and data analysis time, and to improve accuracy, these procedures were automated with a microcomputer system.

Methods Employed: The microcomputer system is a DEC MINC-11/03 (Modular Instrument Computer) containing an LSI-11 microprocessor, 32K words of memory, auxiliary disk storage, and analog-to-digital and digital-to-analog conversion capability. There is also a video graphics display, a keyboard console, a hardcopy unit for printing the video display, and a line printer.

In determining pulmonary compliance, transpulmonary pressure (the difference between alveolar pressure, i.e., mouth pressure with mouth shutter closed, and esophageal pressure, as measured by a balloon transducer swallowed by the patient) and lung volume (measured with a wedge spirometer) are determined by the computer as the physician repeatedly closes a mouth shutter throughout a patient's inhalation or exhalation. A graphical plot of the data and an exponential least squares curve fit of the data are then produced to aid in evaluating the "stretchability" of the patient's lungs.

During the steady state treadmill procedure, the computer monitors expired volume and flow via a Tissot spirometer and pneumotach, respectively, as the patient is subjected to stepped increases in exercise, each time starting from a resting state. Expired oxygen, carbon dioxide, and nitrogen concentrations are monitored via a Perkin-Elmer mass spectrometer gas analyzer. To determine the patient's anaerobic threshold (i.e., point where the body begins to heavily rely on anaerobic metabolism and produce lactic acid), the patient is catheterized in order to obtain arterial

blood samples at each steady state level. Acid/base and gas concentrations are determined offline by a blood gas analyzer from a sample of the patient's arterial blood, and entered at the keyboard. Pulmonary volumes, flows, and oxygen consumption--a measure of how hard the patient actually works to perform a given level of exercise--are then calculated.

When air flow and expiratory gas concentrations can be monitored in realtime, the patient's anaerobic threshold can be determined noninvasively without the need to measure the partial pressure of oxygen in blood via arterial catheterization. Anaerobic threshold is determined from measures of exhaled oxygen, carbon dioxide, and respiratory quotient. Breath-by-breath analysis also allows the performance of nonsteady state exercise testing, where the patient is subjected to continuously increasing levels of exercise to provide a dynamic picture of cardiopulmonary performance.

Progress in FY83: The MINC computer system now is used routinely to perform the static pulmonary compliance and inspiratory muscle strength procedures. Work continued on automating the treadmill exercise system. However, a change in clinical priorities redirected efforts towards the development of a breath-by-breath steady state exercise system rather than simply automating the technique currently performed. A further change in priorities led to curtailing development of the automated exercise system.

Proposed Course: No further work is planned at this time.

Publications:

Nadel, L.D.: Automated Pulmonary Analysis by an Online Microcomputer In Nair, S. (Ed.): *Computers in Critical Care and Pulmonary Medicine* New York, Plenum Press, 1983, pp. 101-113

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		Z01 CT00093-02 CSL
PERIOD COVERED		
October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)		
Anesthesia Computer System		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.)		
(Name, title, laboratory, and institute affiliation)		
Percy S. Plexico, Chief, Project Development Section, CSL, DCRT		
COOPERATING UNITS (if any)		
CC: D. Lees, M.D., Chief, Anesthesia Service. CSL, DCRT: L.D. Nadel, Ph.D., Senior Staff Fellow; R.B. Dew, Electronics Engineer.		
LAB/BRANCH		
Computer Systems Laboratory		
SECTION		
Project Development Section		
INSTITUTE AND LOCATION		
DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS	PROFESSIONAL	OTHER
1.0	1.0	

Anesthesia Computer System

This project involves evaluating improved instrumentation techniques and identifying and investigating ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring and automated recordkeeping in the operating room.

Background and Objectives:

While computers and automation have been used in intensive care settings for some time, little previous work has been reported on their application in operating rooms. Three areas of potential benefit of an anesthesia computer have been identified.

1. Adjunctive monitoring, i.e., using the computer for monitoring and display of patient parameters. The main goals are a unified, easy to read display; limit detection and trend analysis of the parameters; and archiving of the measurements for later use in research or anesthesia mishap analysis.
2. Automated recordkeeping, in which the computer would not only record the results of monitoring, but also make provisions for a record of drug administration, for free text notes by the anesthesiologist, and for producing a printed record suitable for inclusion in the patient's record.
3. Noninvasive determinations of additional parameters relevant to a patient's physiologic status.

An advantage of such a system is that it will allow the anesthesiologist to devote more time to the patient by

simplifying the tasks of observing and recording measurements. An added potential advantage is an intelligent system of alarms to warn of a patient's deteriorating condition. Present alarm systems often are disarmed due to false triggering.

Progress in FY83: The project plan developed last year was expanded to add greater detail. Engineers were assigned to the project and work was formally begun on system development. Using a DEC MINC 11/23 computer system and a Perkin-Elmer MGA 1100 gas mass spectrometer, development of a prototype system for online monitoring and trending a patient's inhaled and exhaled gas concentrations (including gaseous anesthetics) was begun. Only oxygen and end tidal carbon dioxide concentrations can be monitored with present instrumentation. Designs have been prepared and additional equipment ordered to use this system in conjunction with a pneumotach and pressure transducer to derive pulmonary function parameters of a mechanically ventilated patient.

Display technologies/systems were investigated for use in a single consolidated patient display. Available technologies such as voice input and handwritten character recognition were explored as potential means for simplified free text entry into the patient's O.R. record.

Additional parameters, direct and derived, were sought and investigated for incorporation into the existing patient monitoring scheme. The emphasis has been on gathering additional patient information through noninvasive techniques.

Proposed Course: Development of the gas mass spectrometer monitoring prototype system will be completed and clinical usefulness will be evaluated. Next, a pulmonary function capability will be added to the system. We will strive for both trend and realtime display. We then hope to identify available hardware and technology to integrate the various patient parameters into a unified display/automated patient recordkeeping system. Technologies such as voice input will be evaluated for entry of free text information into the system. Necessary hardware will be purchased and a single bed prototype system will be developed

and evaluated. Future plans include streamlining the prototype and developing a multiple operating room monitoring/reporting capability.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00065-04 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (If 50 characters or less, title must fit on one line between the brackets) Medical Information Technology Project		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and medical affiliation) Scott J. Allen, Medical Research Analyst, CSL, DCRT		
COOPERATING UNITS (if any) CSL, DCRT: D.C. Songco, Electronics Engineer; P.S. Plexico, Chief, Project Development Section. Others: C.S. Brown, M.D., Consulting Dermatologist; A.W. Pratt, M.D., DCRT Director.		
LABORATORY Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANTEARS 1.0	PROFESSIONAL 1.0	OTHER

Medical Information Technology Project

This project involves the application of microprocessor technology and improved man-machine interface methods to permit physicians and their associates to communicate more directly with computer record systems. A pilot study involving medical transactions entered directly by practicing physicians is in its second year. The goal is to develop better ways to automate the essential physician contribution to the health care record that is used in both research and patient care.

Background and Objectives: The use of computers in medical and hospital practice is increasing as the cost of systems is decreasing due to technological innovation. However, few physicians are comfortable with current machine interfaces. With this in mind, we are investigating devices and methods that provide a more capable, attractive interface while maintaining an acceptable level of flexibility and efficiency. The aim is to increase physician productivity in patient diagnosis and treatment and to increase patient understanding of disease processes and management plans.

Progress in FY83: In collaboration with two practicing dermatologists, we are field testing an ambulatory patient care transaction system. This system allows the physician to enter, store, retrieve, and disseminate patient data needed by various members of the health care team as well as by the patient. The immediate

data processing focus includes machine generation of patient information and treatment schedules, pharmacy prescriptions, and medical and surgical procedure reports.

Disease-specific and problem-specific protocols are used to lead the user through a restricted tree-structured hierarchy of relevant diagnoses, treatments, drugs, and procedures. Where appropriate, protocols are modified by such factors as patient age, sex, weight, disease stage, and therapeutic response specified by physician. When all workups and treatments are indicated, the computer produces hardcopy treatment plans for the patient, record summaries for the doctor, prescriptions for the pharmacist, and test requests for specified laboratories.

Much of the clinical software is table-driven to allow the physician to add and modify the data bases. This approach also provides a convenient means of adapting the programs to other clinical care and research environments. Both the clinical data base and processing software are being developed and tested on the CSL time-shared computer system. Finished programs, ready for use in patient care, are then transferred to a compatible microcomputer system situated in the physician's office.

Proposed Course: Selected physician-operated modules will be enhanced to support critical diagnostic and therapeutic functions in ambulatory care. Programming logic to support isolated patient encounters also will be expanded to display key data from prior visits. Software modules to help order laboratory tests and prepare physician referral letters will be developed. The conventional CRT and keyboard terminal employed now will be augmented with faster I/O devices that are tailored to this medical application. For example, we plan to use graphic input to facilitate the capture of anatomic disease descriptions and keyboard substitutes to speed menu item selection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00090-02 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Molecular Graphics, Computer Modeling, and Sequence Analysis		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Benes L. Trus, Research Chemist, CSL, DCRT		
COOPERATING UNITS (if any) LFB, NIADDK: A.C. Steven, Visiting Scientist. DB, NCI: P.M. Steinert, Visiting Scientist.		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS 0.1	PROFESSIONAL 0.1	OTHER

Molecular Graphics, Computer Modeling, and Sequence Analysis

The sequence of some regular proteins, together with other structural information such as data from x-ray diffraction, fiber diffraction, electron microscopy, and spectroscopic analysis can be used to evaluate models of the protein structure. Two current studies involve keratin (with NIADDK and NCI) and actin (with NIADDK).

As the sequence of keratin cyanogen bromide fragments becomes available, an analysis of the sequence is proceeding by studying periodicities in the sequence, and by predicting by computer the conformational properties of the specific amino acids in local regions of the chain. It is anticipated that the experimental results may be able to clearly specify if any of the proposed two or three models are correct.

Background and Objectives: It is currently possible convincingly to model and predict the structure of regular (helical) proteins. With the current knowledge of the structure of the collagen helix, synthetic protein analogues of collagen, tropomyosin, and other regular proteins, one can extend this technology to new proteins as the sequence is experimentally determined, if there are known points of similarity.

Significance to Biomedical Research: Many proteins do not form three-dimensional crystalline solids whose structure can be analyzed by classical x-ray diffraction. However, if these proteins are regular, comparison and analogy with related proteins can be used to model the

unknown structures in order to understand the structure and functioning of the proteins. In addition, one can use computer models to analyze two or more possible candidates and determine the most likely protein structure.

Progress in FY83: A new model of collagen has been proposed that reconciles previously diverse data from a variety of experimental sources. A new analysis has begun that will use the sequence of keratin filaments to compare the structure to proposed models, and to other proteins whose structure has been well characterized.

Methods Employed: Standard Fourier methods have been used to analyze the sequences and to cross-correlate sequences. These sequence regularities are usually correlated with structural features, such as the collagen triple helix, the alpha helix, or the tropomyosin double stranded alpha helix. In addition, software was written to model the collagen helix and double stranded alpha helices on the Evans and Sutherland Picture System. This unique hardware allows three-dimensional analysis of proposed structures, both using traditional wire models, and by using CPK "ball" models in three dimensions, where the size of the ball is related to the size of the individual amino acid, and the color of the ball is related to the function of the amino acid.

Proposed Course: As new sequences of regular (helical) proteins become available, it is relatively easy to model these sequences and describe their structures both graphically and quantitatively.

Publications:

Steinert, P.M., Rice, R.H., Trus, B.L., and Steven, A.C.: Complete Amino Acid Sequence of a Mouse Epidermal Keratin Subunit: Implications for the Structure of Intermediate Filaments. *Nature* 302: 794-800, 1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00080-03 CSI
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the hyphens) Computer Analysis of Gel Electrophoresis		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Benes L. Trus, Research Chemist, CSI, DCRT		
COOPERATING UNITS (if any) LBP, NIADOK: R. Goldman, Staff Fellow.		
LAB BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANY YEARS 0.1	PROFESSIONAL 0.1	OTHER

Computer Analysis of Gel Electrophoresis

This project was designed to allow NIH scientists to easily and accurately quantitate one- and two-dimensional gels. Quantitative comparisons of two gels is semi-automatic, and one project has used methods developed here to separate the results of double-labeled radiography of protein gels using color negative film and appropriate filters. This is possible because tritium and spillover of carbon 14 are recorded in the blue sensitive layer of the film while carbon 14 alone is recorded in the green or red sensitive layer. This method was used to analyze the effect of growth rate and medium composition on the relative levels of individual proteins in a pathogenic strain of *Escherichia coli*.

Background and Objectives: The primary objective of this project has been to develop experimental techniques and computer software to easily and automatically quantitate two-dimensional gels. In addition, analysis of one-dimensional gels is equally accurate and feasible. Initially only Coomassie blue stained gels were analyzed, but currently autoradiographs are equally amenable to processing.

Significance to Biomedical Research: Use of gel electrophoresis and autoradiographs is commonplace in chemical, biochemical, and biomedical research. However, the quantitation of these gels is difficult. We have developed systems that accurately and easily provide this quantitation to the scientist. A number of

laboratories outside of NIH have requested our software for private use.

Progress in FY83: This project has produced many useful results to a number of scientists at NIH. As new gels require analysis, further fine tuning of the methods will continue to improve the product. In addition, we have used the methods to analyze color negative film (rephotographed through appropriate color filters) so as to analyze the growth rates and medium composition on the relative levels of individual proteins in a pathogenic strain of *Escherichia coli*. These results are being submitted for publication.

Methods Employed: Gels were rephotographed onto Ektapan 4162 black and white film. Color films were photographed through appropriate color filters. The black and white negative was scanned on the Perkin-Elmer microdensitometer and stored on tape for later processing. A computer program CINT was used to analyze the two-dimensional gels, and another program OVERLP was used to correlate two gels when necessary or desired. PIC was used in the one-dimensional analyses.

Proposed Course: Computer software is being expanded to provide for better matching of two gels, and all software is essentially machine independent for transfer to the newly acquired image processing laboratory. Additional options are being added to the software to provide additional flexibility to the research scientist.

Publications:

- Goldman, R.C., Leiva, L., and Trus, B.L.: Quantitative Double-Label Radiography of Two-Dimensional Protein Gels Using Color Negative Film and Computer Analysis. *European Journal of Biology* 131: 473-480, 1983
- Nikodem, V.M., Huang, D.R., Trus, B.L., and Rall, J.E. The Effects of Thyroid Hormone on In Vitro Phosphorylation, Acetylation, and Ribosylation of Rat Liver Proteins. *Hormone and Met. Res.* (in press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00091-02 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Morphometric Analysis of Normal and Neoplastic Tissue Cultures		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Benes L. Trus, Research Chemist, CSL, DCRT		
COOPERATING UNITS (if any) ICMB, NCI: K.K. Sanford, Chief, In Vitro Carcinogenesis Section; W. Taylor; G. Jones, Microbiologist; M. Weedon, Laboratory Technician.		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.1	PROFESSIONAL 0.1	OTHER

Morphometric Analysis of Normal and Neoplastic Tissue Cultures

This project was designed to study the morphometric differences between normal and tumorigenic fibroblastic cell lines. Initially, human, rat, and mouse cell lines were selected for analysis. The cells were photographed from living cultures without staining or fixing. The types of criteria being used by the computer to aid in differentiating between normal and tumorigenic cells include nucleus and nucleolus size and shape, and chromatin texture and clumping.

Background and Objectives: This project, which was begun this year, uses standard techniques of image processing as applied to these low contrast unstained specimens as well as techniques developed at NIH. We hope to demonstrate that it is possible and practical to differentiate between normal and tumorigenic cells in a nondestructive manner. We are using many of the same criteria used by pathologists in differentiating stained and fixed sections.

Significance to Biomedical Research: We hope to demonstrate that this nondestructive method can be used with confidence to determine if a culture is normal. This method would be important for studies of carcinogenesis in cultures.

Progress in FY83: We have developed software to perform a pilot study on three types of cultures. Preliminary results suggest that we are able to determine statistical differences between normal and abnormal cells.

Methods Employed: Cell cultures were photographed through a light microscope onto 35mm black and white film. The film was digitized by a Perkin-Elmer 1010G microdensitometer with a 50 square micron aperture. Images were viewed on a video frame buffer and processed interactively. Results are stored in log files for each sample, and files are pooled for each type of culture, yielding better statistics. The mouse and rat cultures underwent spontaneous neoplastic transformation, while the human fibroblast line was exposed to chemical carcinogens to generate the tumorigenic line.

Proposed Course: After the analysis of the three pilot studies, we expect to continue analysis of additional cell lines, and are considering nonlethal staining techniques.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00092-02 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Virus Structure as Determined by Image Processing of Electron Micrographs		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Benes L. Trus, Research Chemist, CSL, DCRT		
COOPERATING UNITS (if any) IPB, NIADOK: A.C. Steven, Visiting Scientist.		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.4	PROFESSIONAL: 0.4	OTHER:

Virus Structure As Determined by Image Processing of Electron Micrographs

A new virus structure, that of bacteriophage T7, has been published. The structure was determined by image processing of electron micrographs. We analyzed T7 polycapsid tubes because these structures are more amenable to image processing. Optical diffraction revealed that the polycapsids were based on cylindrical foldings of a hexagonal lattice with a spacing of 12.6 nm, which is similar to the lattice constant for other complex icosahedral phage capsids defined to date. However, the details of the T7 capsomer differ from the other results.

Background and Objectives: Virus shells are composed of one or a few proteins that form simple repetitive geometric forms. The forms or containers can be, for example, cylinders, icosahedra, or spheres. There are classes of structures, and knowledge of the fine structure of one coat protein can be used to understand the structures of other similar viruses in the class. It is our primary objective to add to the pool of information, and to be able to use this information to increase our understanding about how virus structure relates to function and activity.

Significance to Biomedical Research: Viruses are significantly smaller than bacteria, and as a result are not seen in a light microscope. Information about their structure usually comes from electron microscopy, which is limited by resolution, low contrast, and noise. If staining is used, then the resolution is limited by the size of the stain, and often has noise as a result of uneven staining. However, because virus structures are generally periodic, they are a perfect candidate for image processing. This project should be considered as basic research whose aim is to increase our understanding of the structure and functions of viruses in general, as well as subclasses of viruses similar to those studied to date.

Progress in FY83: The results of a virus previously determined by us, beet necrotic yellow vein virus, have been published. In addition the results of the structural determination of the T7 virus have been presented at two meetings, and are being submitted for publication. These results are especially significant because another virus (polyoma) that has significant similarities to T7 recently has been reported to have significantly differing geometry.

Methods Employed: The micrographs were taken with a Philips EM400T microscope, and the best negatives were preselected by optical diffraction. Negatives were digitized on a Perkin-Elmer 1010G microdensitometer and analyzed by means of the PIC computer system. Results were photowritten on the Perkin-Elmer microdensitometer. Typical processing of the images consisted of Fourier filtering of up to 50-unit cells and symmetrization of the results as needed.

Proposed Course: We anticipate evaluating other viruses for suitability for examination with these methods, and continuing with this ongoing project to determine the structure of various classes of viruses.

Publications:

Steven, A.C., Serwer, P., Bisher, M., and Trus, B.L.: Molecular Architecture of Bacteriophage T7 Capsid. *Virology* 124: 109-120, 1983

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		Z01-100002-03 CSL
PERIOD COVERED		
October 1, 1982 to September 30, 1983		
TITLE OF PROJECT and character of task. This must fit on one line between the borders		
Image Processing of Electron Micrographs		
PRINCIPAL INVESTIGATOR. List other professional personnel on subsequent pages		
(Name, title, laboratory, and institute affiliation)		
Benes L. Trus, Research Chemist, CSL, DRT		
COOPERATING UNITS (Name, title, laboratory, and institute affiliation)		
W.A. Hagins, Chief, Section on Membrane Biophysics; M.C. Foster, IPA Appointee/		
Guest Worker; J.C. George, Laboratory Technician. PSI, DRT; S.D. Lesham,		
Senior Staff Fellow, Other: E. Foster, Univ. of Colorado & Fogarty Scholar.		
LABORATORY		
Computer Systems Laboratory		
SECTION		
Systems Design Section		
INSTITUTE AND LOCATION		
DRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS	PROJECT BUDGET	OTHER
0.2	0.2	

Image Processing of Electron Micrographs

This project was designed to facilitate structure determination from electron microscopy by providing suitable software, hardware, and scientific expertise to allow other scientists, primarily at NIH, to use image processing and computer reconstruction to determine or understand a specimen's structure.

Two new applications that began this year are analysis and identification of small particles by electron beam excited x-ray microanalysis as applied to aqueous suspensions of vertebrate retinal rod cells and the analysis of the microtrabecular lattice and the cytoskeleton to determine their volume, surface area, and the diffusion of molecules through it.

Studies continued from FY82 include analysis of keratin, membrane structure, and muscle structure.

Background and Objectives: The objective of this project is to develop a general-purpose software package for the analysis of electron micrographs. In addition, the computer analysis requires optimal utilization of the available hardware and the availability of a research scientist capable of providing logistical

support. Techniques and software developed in this project have been used elsewhere both at NIH and at other laboratories.

Significance to Biomedical Research: Computer analysis of electron micrographs is still a relatively recent addition to the tools available to scientists for structural analysis. Few laboratories have the combined software and hardware capability to perform the image processing and image reconstruction available at NIH. These techniques are especially powerful when applied to two-dimensional crystalline structures. In addition, we can correlate and align similar particles that are not crystalline, and correct for a number of artifacts and experimental problems.

Progress in FY83: This project has had some growth in software, but primarily has grown in the utilization of programs and the PIC system. It is feasible for an NIH scientist to bring in a problem and obtain preliminary results in a relatively short period of time. Then a decision is made to expand the preliminary study into a project, or to use the results obtained.

One study, in collaboration with NIADDK, used the computer to examine digital information to examine small particles by electron beam excited x-ray microanalysis for particles in aqueous suspension. This novel approach was applied to the isolated outer segments of vertebrate retinal rod cells and was used to study the distribution of potassium, osmium, phosphorus, and calcium 45 in unstable objects.

Another study, in collaboration with PSL, DCRT, studied the microtrabecular lattice and the cytoskeleton. Images were digitized and analyzed for the fraction of interlinked slender strands versus the amount of open spaces.

Proposed Course: This project will continue software development as needed, and will be converted to use the new image processing facility as it becomes available. In addition, as new biological structures become available for analysis, these will be examined.

Publications:

Foster, M.D., George, J.S., Trus, B., and Hagins, W.A.: Na, K, Ca, Mg, and Exchangeable Ca(45) ions in Rod Outer Segments by Combined X-ray Microanalysis and Radioautography. *Biophysical Journal* 41(2): 341, 1983.

Gershon, N., Porter, K., and Trus, B.: The Cytoplasmic Matrix: Its Structure, Volume, Surface Area, and Space for Diffusion. *Biophysical Journal* 41(2): 85, 1983.

Gershon, N. D., Porter, K. R., and Trus, B. L.: The Microtrabecular Lattice and the Cytoskeleton. Their Volume, Surface Area and the Diffusion of Molecules Through It. *Journal of Cell Biology* 95(2): 406A, 1982.

Gershon, N. D., Porter, K. R., and Trus, B. L.: The Microtrabecular Lattice and the Cytoskeleton. Their Volume, Surface Area and the Diffusion of Molecules Through It. In Oplatka, A., and Balaban, M., (Eds.): *Biological Structures and Coupled Flows*. New York, Academic Press, 1983, pp. 377-380.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER
		Z01 CT00061-04 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Electron Microanalysis Facility		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Keith E. Corliss, Electronics Engineer, CSL, DCRT		
COOPERATING UNITS (if any) BEIB, DRS; C.E. Flori, Physical Scientist; C.C. Gibson; H.S. Eden; J.R. Ellis; C.R. Hook; R.D. Leapman; C.R. Swyt. CSL, DCRT; J.S. Del Priore, Mathematician; P.S. Flexico, Chief, Project Development.		
LABORATORY Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS 1.5	PROFESSIONAL 1.5	OTHER

Electron Microanalysis Facility

CSL is collaborating with BEIB, DRS, in developing an automated electron microanalysis facility consisting of two electron microscopes interfaced to a computer system. The facility is being used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL designed and implemented the computer system, which acquires and displays the spectra and images produced by Electron Energy Loss Spectrometry, Energy-Dispersive x-ray Spectrometry, and Wavelength Dispersive x-ray Spectrometry.

See also:

Z01 RS10058-05

Z01 RS10059-05

Background and Objectives: The Computer Systems Laboratory designed and implemented a computer system as part of the BEIB Electron Beam Imaging and Microspectroscopy Facility. The facility consists of two electron microscopes, and is being used for research into the elemental composition of biological specimens

and for developing new techniques in electron microscopy.

One of the electron microscopes is an Hitachi H-700H 200 keV Scanning Transmission Electron Microscope (STEM) equipped with:

- a lithium-drifted silicon (Si(Li)) detector connected to a Kevex 7000 Analytical Spectrometer for performing Energy-dispersive x-ray Spectrometry (EDS)
- an electron spectrometer for performing Electron Energy Loss Spectrometry (EELS)
- detectors for bright and dark field electron current signals.

The other electron microscope is a Cameca 50 keV Electron Microprobe equipped with:

- a Si(Li) detector for performing EDS
- three Wavelength Dispersive x-ray (WDS) spectrometers
- detectors for bright and dark field electron current signals.

The PDP-11/60 computer system interfaced to both microscopes performs the following functions:

- control electron beam position, stage position, and the various detectors
- acquires spectral and image data from all detectors
- process and display the spectral and image data
- monitor and display a wide variety of "housekeeping" parameters, including: lens currents, lens temperatures, beam current, beam energy, pump temperatures, coolant flow, vacuum pressures, water leak detectors, power supply voltages, room temperature, and room humidity.

Progress in FY83: This year both EEL and EDS imaging were made operational. These techniques are now in routine use on many biological research projects. The EEL images are the first successfully produced on a STEM and the first to be properly compensated for mass-thickness effects.

A new technique was implemented for background-correcting EDS images by applying a top-hat digital filter to the EDS spectrum at each pixel. The presentation of this technique at the 1982 Joint

National Meeting of Electron Microscopy Society of America and the Microbeam Analysis Society won the Corning award for the best contributed scientific paper.

EEL imaging was improved later in the year by using the satellite computer to track the position of an energy loss edge and to compensate for spectrometer drift. This permits images to be acquired over longer periods of time, thus allowing elements to be imaged at lower concentrations.

Work has begun on a more sophisticated method of processing EEL spectra that should further improve EEL image quality.

The WDS and current signal detectors on the Cameca Microprobe were interfaced to the existing data acquisition satellite so that images can be acquired from these detectors by the same software that is used for the STEM. This arrangement was used to produce aluminum images of neurofibrillary tangles in the brains of victims of Amyotrophic Lateral Sclerosis and to produce magnesium images of lymphocytes. Addition of a second satellite dedicated to the microprobe is planned.

The image display and processing capabilities of the system also were improved greatly this year. The DeAnza display system was upgraded by the addition of a Digital Video Array Processor, a Fourth image memory channel, a digitizing tablet, and an 8-bit graphics overlay channel.

The Digital Video Array Processor (DVP), which can perform simple operations (such as add, subtract, and shift) on digital images at video rates, was used to:

- dynamically scale current signal images as they were loaded into the display system;
- implement a four-function "image calculator", used for applying background and other corrections;
- rapidly smooth images via spatial convolution; and,
- calculate pixel density histograms of arbitrary regions.

The digitizing tablet provides a powerful and convenient operator interface. All of the previous functions plus many others such as scroll, zoom, contrast enhance, intensity transform, region outline, annotate, save, and

restore can be activated and controlled using the tablet.

The forms used to control data acquisition and image display were improved and put into production use. New forms for modifying data acquisition parameters were implemented.

The large amount of data produced from the two microscopes, together with the limited amount of available online disk storage, required the design and implementation of two new data maintenance utilities: ARCHIVE and AUTOBACK. The ARCHIVE utility provides a convenient way for users to move the data from completed or dormant projects to tape. A directory of ARCHIVE tapes and the files they contain is maintained online and can be listed or searched. The AUTOBACK utility provides protection from disk disasters. It manages a set of tapes that are used for periodic full and incremental backup of the system and data disks.

Last, the operating system was updated from RSX-11M V3.2 to RSX-11M V4.0, the most recent release.

Proposed Course: Next year, we expect to enhance the data acquisition software and improve the interface to the Cameca Electron Microprobe.

Publications:

Gorlen, K., Barden, L., Del Priore, J., Kochar, A., Fiori, C., Gibson, C., and Leapman, R.: A Data Acquisition System for an Analytical Electron Microscope. *Proceedings of the FALL DECUS* (in press).

Leapman, R., Fiori, C., Gorlen, K., Gibson, C., and Swyt, D.: Combined Elemental and Structural Imaging in a Computer Controlled Analytical Electron Microscope. *Journal of Ultramicroscopy* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00057-04 CSL
PERIOD COVERED October 1, 1982 to September 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Molecular Interactions Laboratory Data System		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and Institute affiliation) Ramon L. Tate, Ph.D., Computer Specialist, CSL, DCRT		
COOPERATING UNITS (if any) MDB, NHLBI: J.C. Osborne, Ph.D., Research Chemist. CSL, DCRT: A.R. Schultz, J.R., Head, Processor Design Section.		
LAB/BRANCH Computer Systems Laboratory		
SECTION Processor Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS: 0.2	PROFESSIONAL 0.2	OTHER:

Molecular Interactions Laboratory Data System

This microcomputer (PDP 11/03) data system supervises the acquisition and processing of information from an analytical ultracentrifuge and a circular dichroic spectropolarimeter used in MDB, NHLBI, to investigate the interactions between human lipoprotein subunits. Current capabilities include acquisition, display, and preprocessing of data from the ultracentrifuge and transfer of preprocessed data files to the DECsystem-10 for further analysis under MLAB using predefined procedures invoked by a few simple commands. Software support for the spectropolarimeter includes the ability to add, subtract, and average CD spectra and to transfer files to the PDP-10 for further analysis. Enhancements this year include installation of a four-pen digital plotter and a companion DECsystem-10 software package for generating plots of CD and ultracentrifuge data. Completion of this project is anticipated when modifications to the ultracentrifuge interface are finished to provide greater noise immunity.

Background and Objectives: As a supplement to the ultracentrifuge data system, a microcomputer-based data acquisition and analysis system was developed for use with a Cary Model 61 CD spectropolarimeter. The system consists of a simple, flexible CD spectropolarimeter/microcomputer interface and an interactive data processing program system by which CD spectra may be acquired, averaged, subtracted, converted to mean residue ellipticities, printed, and stored for future use. Stored data may also be

transferred conveniently to a large computer facility for semi-automatic conformation analysis. The system overcomes some of the difficulties encountered in attempting the visual interpretation of noisy CD spectral recordings and in providing additional data manipulation capabilities not easily realizable with manual methods. The CD spectropolarimeter is interfaced with the microcomputer system via a special highly noise-immune interface scheme based on the conversion of the signals from the spectropolarimeter to pulse trains. These pulse trains are then transmitted via current loops to a CSL-designed timer/counter interface board in the microcomputer. The operating software consists of two programs that interact with the user through a standardized combination of menus and dynamically alterable displays. One program provides data acquisition, processing, output, and storage functions, while the other program provides all but acquisition and includes the capability to edit the operating parameters of a scan file stored on the diskette.

Progress in FY83: Support for a four-pen digital plotter was added this year, including hardware reconfiguration that permits system operation with or without the plotter online. Software support also provided includes MLAB-based routines for plotting both CD and ultracentrifuge data with or without smoothing.

Proposed Course: Future additions to the system will be restricted to further modification of the ultracentrifuge interface to provide greater noise immunity, at which time the project will be considered completed.

Publications:

Tate, R.: *Microcomputer Systems in the Laboratory: An Introduction*. Serono Symposium Series, Raven Press, 1983 (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		Z01-TOX158-04-151
PERIOD COVERED		
October 1, 1982 to September 30, 1983		
TITLE OF PROJECT: <i>Californium-252 plasma desorption mass spectrometer data system</i>		
PRINCIPAL INVESTIGATOR: <i>Californium-252 Plasma Desorption Mass Spectrometer Data System</i>		
(Name, title, laboratory, and multiple affiliations)		
Ronald E. Tate, Ph.D., Computer Specialist, CSI, NIE		
COOPERATING UNITS (if any)		
LC, NHLBI: H.M. Fales, Ph.D., Chief.		
LAB BRANCH		
Computer Systems Laboratory		
SECTION		
Processor Design Section		
INSTITUTE AND LOCATION		
DRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS	PROFESSORIAL	OTHER
0.5	0.5	

Californium-252 Plasma Desorption Mass Spectrometer Data System

The Californium-252 plasma desorption mass spectrometer puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Realtime performance and the ability to access very large data arrays in main memory are key considerations. After delays necessitated by hardware design problems, software upgrades, and facilities renovations, both the spectrometer and a data system design modeled after one in use at Texas A & M University have been installed and are now functional. This instrument now provides NIH the capabilities of mass analysis for compounds that have proven difficult or impossible to analyze by other mass spectrometric means. It also extends the range of mass analysis to compounds with molecular weights in excess of 5000.

The Californium-252 time-of-flight (TOF) mass spectrometer employs nuclear fission fragments to ionize samples that frequently have proven intractable to other methods of analysis. The TOF mass spectrometer, which is not commercially available, was developed at Texas A & M University by Dr. Ronald Macfarlane under an NHLBI contract.

Background and Objectives: In this instrument, fission fragments generated by the radioactive decay of a thin film of ²⁵²Cf impact on a thin layer of sample deposited on a conductive plastic film, producing a localized plasma. The sample molecules produced

within this plasma are extracted by an electric field and briefly accelerated down an evacuated tube toward a microchannel plate ion detector. The elapsed times between the ionization event and the arrival of the ions produced are measured with an ultraprecise clock capable of measuring time intervals of hundreds of milliseconds with a resolution of 800 picoseconds. The elapsed time measurements are then sent to a computer where they are sorted, tallied, converted to mass units, and displayed. The extended range of the timing clock coupled with the unique characteristics of the ionization process make this mass spectrometer ideally suited to the investigation of the high molecular weight compounds typical of biological materials. The data system was specified to be compatible with interface hardware and software available from Dr. Macfarlane. The need for realtime sorting of a large volume of input data puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Realtime performance and the ability to access very large data arrays in main memory are key considerations.

Progress in FY83: Numerous problems related to implementing the software written at Texas A&M on the newer model computer being used in Dr. Fales' Laboratory slowed progress toward a fully functioning system. The computer system was expanded to include a line printer and an additional 256K bytes of memory. Modifications were also made to the mass spectrometer to enhance its safety and reliability.

Proposed Course: The anticipated addition of a direct memory access channel controller dedicated solely to the mass spectrometer interface will permit simultaneous data acquisition and processing. An upgrade of the mass spectrometer interface first-in/first-out (FIFO) buffer to provide greater speed and reliability is also planned. Software-related goals include the reorganization and completion of system implementation documentation and the training of Laboratory of Chemistry personnel in system maintenance procedures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES-PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00056-04 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Distributed Laboratory Data Acquisition and Control System		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) John I. Powell, Electronics Engineer, CSL, DCRT		
COOPERATING UNITS (If any) LCP, NIADK: W.H. Jennings, Physicist, CSL, DCRT; E.R. O'Bryan, Electronics Engineer; A.R. Schultz, Jr., Chief, Processor Design Section; D.C. Carpenter, Electronics Engineer, Syntex, Inc.; J.T. Morris, Programmer.		
LAB/BRANCH Computer Systems Laboratory		
SECTION Processor Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MONTHS 4.0	PROFESSIONAL 4.0	OTHER:

Distributed Laboratory Data Acquisition and Control System

An integrated laboratory data acquisition and processing system has been developed for LCP and LMB, NIADK. The system is configured with satellites coupled through a local network to a host processor. At each satellite a dedicated microcomputer system performs data acquisition from and control over an instrument/experiment. Although acquired data files may be stored locally, they are normally transferred via the network to a host storage medium. The local network allows the host storage medium to appear as a "virtual" storage device to the satellites. The hub of the network, the concentrator, utilizes DMA hardware on all communications links and performs a file store and forward function. Processing software provided at the host allows LDACS data files to be: added, subtracted, averaged, smoothed, baseline corrected, integrated, differentiated, multiplied by a constant, and added to a constant. The results may be displayed graphically on a Tektronix terminal, typed at a terminal, printed on the line printer, plotted on an X-Y plotter, or transmitted to the NIH DECSys-10 for additional processing.

Background and Objectives: A system of microcomputers capable of independently controlling and acquiring data from an instrument/experiment was proposed in December 1976 as the best system architecture for upgrading laboratory data processing. Initially a prototype laboratory data acquisition and control system (LDACS) computer and essential

elements of the communication system were developed to verify system performance.

A satellite includes a Digital Equipment Corporation (DEC) LSI-11 microcomputer, 28K words memory, low density random access storage, graphics terminal, and all the necessary I/O hardware to interface the instrument/experiment. Software developed by CSL for each satellite, running under DEC's RT-11 operating system, provides the user with a "turn-key" system. Presently the system is configured with nine satellites, supporting thirteen instruments, connected (via the concentrator) to a DEC PDP 11/70 host processor. Instruments connected to the network include: Spectrophotometers, Cary 14, Cary 118, Cary 210, Cary 219, two Perkin-Elmer 580B's, a microspectrophotometer (designed by NIADCK); Spectropolarimeters, Cary 60, Jasco J500A; a Varian Electron spin resonance spectrometer; I.S. Co. Model 1440 liquid chromatograph; a SPEX spectrometer (utilizing EG&G model 1420 intensified silicon photodiode array detector and model 1218 detector controller); and a stimulus response retina experiment.

The local network includes a software module, installed as a handler under the RT-11 operating system, at each satellite. Each satellite is connected via a hardwired serial link to a front end concentrator. The concentrator performs a file store and forward function. Received files are placed on a first-in/first-out queue. Files are transferred from the queue to the host via a parallel DMA link. The communications task running on the host maps the files to the appropriate directory area based on the identity of the satellite that originated the transfer and the extension of the file being transferred.

The host processor, a DEC PDP 11/70, is configured with: 640K words of memory, a high speed printer/plotter, an X-Y plotter, a 9 track magnetic tape drive, dual floppy disk drives, and two large capacity disk drives. DEC's multiuser, multitasking operating system, RSX-11M, is used to service the processing needs of the users. User access to the host is provided by hardwired links between terminals and host timesharing ports.

Progress in FY83: A satellite, supporting data acquisition from and control over a Cary 210

spectrophotometer, was added to the system in FY83. LDACS software supporting acquisition of data from an EG&G 1420 Intensified Silicon Photodiode Array Detector and 1218 Solid State Detector Controller (used with a SPEX spectrometer) was written and installed. The EG&G instrument shares an LDACS with a Perkin-Elmer 580B. Software was provided for an experimental setup on the Varian ESR for studying red blood cell deformability (spectral change) under sheer stress. In addition to acquiring data from the ESR, the LDACS controls blood flow rates during the experiment. "Melting Run" programs, incorporating a modified Lauda S-1 bath temperature controller that allows computer control of the bath temperature, were provided for the Jasco 500A, Cary 118 and 210, both Perkin-Elmer 580Bs, and the EG&G 1218.

The general processing programs on the PDP 11/70 were improved to make them easier to use and to extend their capabilities. Many processing applications now are written as CLI indirect command files, which prompt the user for necessary information, compose task command files and then initiate the processing program, passing it the task command file.

Two RA81 fixed Winchester disk drives and one RA60 removable disk drive were ordered to replace the PDP 11/70's two RP04 system disks. This configuration will increase the online storage capacity by 500 percent, sufficient to service the current and projected requirements of this computing resource. An RL02 cartridge disk drive was ordered to provide a convenient mechanism for long term individual data archival.

User's manuals for the Jasco 500A, EG&G 1218, Varian ESR, Cary 210, and Cary 118 were provided.

Proposed Course: Support for the system will continue. The retrofitting of LDACS units with up-to-date software and system documentation will be completed. The original scope of the project (upgrading of the H-516 centralized system) has been completed. However, it is anticipated that some level of long term support will continue. New satellites or instruments may be added to the system, and existing LDACS acquisition programs may be modified to enhance data acquisition or to

incorporate new intruments/experiments. Occasionally special purpose programs to process a set of experimental data may be required.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00103-01 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Personal Computers in Laboratory Applications		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) David C. Songco, Electronics Engineer, CSL, DCRT		
COOPERATING UNITS (if any)		
LAB/BRANCH Computer Systems Laboratory		
SECTION Project Development Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.4	PROFESSIONAL 0.4	OTHER

Personal Computers in Laboratory Applications

Personal computers are a viable alternative to assembling board level microcomputer systems. They offer the opportunity to select from a wide array of hardware and software. We are developing systems based on the IBM Personal Computer to be used alone and in clusters to serve as realtime data acquisition and control devices as well as terminals to the central facility.

Background and Objectives: CSL has utilized microcomputers since early 1974 for realtime data collection and processing. Personal computers have become a viable alternative to these board level systems in many applications. It is now possible to build upon a wide array of products available from many vendors. With the addition of A/D and D/A modules, personal computers provide the basis for programmable data acquisition and control systems. While a number of personal computers can be used effectively in laboratory situations, CSL, as part of the OD/DCRT Personal Workstation Project, is giving particular attention to the IBM PC.

Progress in FY83: The IBM PC was chosen because of the extensive number of compatible products available from many vendors. With these devices it is possible for a user to acquire data, control experiments, process

data locally, and act as a virtual terminal to the central facility for file transfer and additional processing.

Proposed Course: We plan to evaluate laboratory interfacing hardware and software for the IBM PC so that we can better assist users in configuring it for laboratory applications. We also plan to cluster several PC's in a local area network. In this manner, multiple users can access a common data base while still taking advantage of the rapid response of local processing and displays. The system described under CSL's Medical Information Technology Project is a possible candidate for testing this concept.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER 201 CT00064-04 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Image Processing Facility		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Daniel Syed, Chief, Systems Design Section, CSL, DCRT		
COOPERATING UNITS (if any) CSL, DCRT: V.L. Rizzo, Electronics Engineer; A.J. Pashayan, Computer Specialist; B. Trus, Research Chemist.		
LAB/BRANCH Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS 2.1	PROFESSIONAL 2.1	OTHER

Image Processing Facility

This project provides a utility to display and analyze digital images. The system consists of a powerful 32-bit computer with a mixture of medium resolution and high resolution displays. A high resolution microdensitometer allows precise digitization of x-rays, micrographs, and other images. The computer and peripherals were installed; the first display station was operational in January 1983.

Background and Objectives: This project arose in response to a critically overcrowded situation that exists on the present DCRT graphics computer. As image processing applications at NIH increased, the limited resources of that graphics system became saturated. During FY80, CSL, in collaboration with present and potential users designed a new general purpose computer facility to aid the acquisition, display, and analysis of images such as election micrographs,

CAT scans, and radiographs. During FY83, the system was installed and programmed. The first display station is now in use, providing the functions of the old graphics computer with an order of magnitude increase in efficiency.

Progress in FY83: The system is based on a 32-bit, two megabyte computer, with a smaller 16-bit processor to handle image acquisition. A multidisplay raster scan frame buffer will provide several users concurrent access to the central processor. Images are digitized through a microdensitometer. Hardcopy will be provided by a camera system.

Most of the hardware has been installed, checked, and integrated into a system. Software has been written to provide one user station, and connection of the two computers is complete.

Significance to Biomedical Research: Study of images obtained in the biomedical laboratory is proving more and more fruitful as technology is able to supply the proper tools at a reasonable cost. Biomedical scientists are employing image analysis for a wide variety of research goals, and the use of such techniques is expected to grow very rapidly in the near future.

Proposed Course: Two more components are on order and will be delivered early next year: an additional two user stations, and microprocessor control for the microdensitometer. These items will be installed and integrated when delivered. Further development of systems and applications software is anticipated.

This project is concerned with the minimization of the number of information carrying units used to represent a medical image in order to improve the efficiency of transmission and storage of such images. Various image data compression techniques and their application to medical images are being evaluated with regard to the amount of compression attained and the quality of the reconstructed image. Methods for implementing these techniques suitable to the clinical environment are being developed.

Background and Objectives: Recently, there has been an increase in the number of medical imaging techniques that result in a digital image representation including computed tomography, nuclear medicine, positron emission tomography, ultrasonography, nuclear magnetic resonance, and digital radiography. As a result of this increased number of digital images, there is a need for Picture Archive and Communication Systems (PACS) that are capable of storing, transmitting, and displaying such images. Because the quantities of image data are large, it is important to consider techniques for data compression to reduce archival storage requirements as well as transmission rate constraints.

Progress in FY83: This project was initiated late in FY83. During this time, the type and characteristics of the medical images that need to be compressed and the techniques that are used presently for image data compression were investigated.

Significance to Biomedical Research: The results of this project will be used in a PACS for the NIH Clinical Center and can benefit any medical center that needs to store and transmit a large number of medical images.

Proposed Course: Various image data compression techniques and their application to medical images will be evaluated with regard to the amount of compression attained and the quality of the reconstructed image. Methods for implementing these techniques suitable to the clinical environment will be developed with consideration given to the time required for compression and decompression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER ZDI CT00105-01 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (60 characters or less. Title must fit on one line between the borders) Medical Image Data Compression		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Robert L. Martino, Ph.D., Electronics Engineer, CSL, DCRT		
COOPERATING UNITS (if any) CSL, DCRT: D. Syed, Head, Systems Design Section.		
LABORATORY Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS 0.1	PROFESSIONAL 0.1	OTHER

Medical Image Data Compression

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00097-02 CSL
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (20 characters or less. Title must fit on one line between the borders.) Analytic Models of Computer System Performance		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Robert L. Marino, Electronics Engineer, CSL, DCR		
COOPERATING UNITS (if any) Un. of MD: R. W. Newcomb, Professor, Electrical Engineering Department.		
LABORATORY Computer Systems Laboratory		
SECTION Systems Design Section		
INSTITUTE AND LOCATION DCR, NIH, Bethesda, Maryland 20205		
TOTAL MONTHS 0.1	PROFESSIONAL 0.1	OTHER

Analytic Models of Computer System Performance

This project involves the development of analytic models that can be used to evaluate the performance of computer systems. During the past year, the work on modeling and analyzing computer systems using the graph theoretic model called Timed Place-Transition (P-T) Nets was continued. This included the development of new methods for determining net invariants and new models for demonstrating the dynamics of computer systems. Detailed models of computer bus control techniques and the operation of a commercial array processor were constructed. These models were analyzed using a method that was developed for evaluating computer system performance with Timed P-T Net models. CSL continued to develop a state variable P-T Net model of the interconnection of two or more microprocessors that provides a framework for determining the avoidance of deadlock and the maintenance of throughput in multiple microprocessor systems. In FY84, Timed P-T Nets will be used to develop more analytic tools for evaluating computer system performance.

Background and Objectives: There are two major approaches to evaluating the performance of a computer system: simulation and analytic modeling. Simulation models have been a popular form of modeling for years but can be difficult and costly to construct, validate, and run. Recent advances in analytic modeling techniques, which can be used to model many aspects of a computer system, have

provided new tools for evaluating computer system performance.

There are two major types of analytic modeling techniques: graph theoretic and queueing theory models. A number of graph theoretic models have been found to be useful for the analytic modeling of computer systems. These include such graph models as Place-Transition (Petri) Nets, Parallel Program Schemata, Computation Graphs, and Marked Graphs. Queueing theory models have also been found to be useful for the modeling of computer systems because they can capture important features of actual systems, and algorithms that solve the equations of these models are available as queueing network evaluation packages.

These analytic models provide useful tools when designing computer systems and deciding among alternative hardware or software configurations. In particular, with the integrated circuits that are currently available, it is technically and economically feasible to build systems consisting of many central processing units. Many processor and memory configurations are also possible now that memories can be placed in close proximity to the processors. Methods are needed for designing systems now possible with this new technology. Various structures have to be considered and analytic methods for evaluating alternatives developed.

Methods Employed: Timed Place-Transition (P-T) Nets are the modeling technique used to develop tools for evaluating computer system performance. The advantages of modeling with these nets are that: large and complex systems can be represented in a manner that is easy to understand due to the graphical and precise nature of these nets, the behavior of the modeled system can be analyzed using developed results of the P-T Net theory, and a system can be synthesized hierarchically with the ability to use different levels of abstraction and refinement. In addition, the usefulness of P-T Nets as models results from their ability to represent both concurrency and conflict in a system. Concurrency occurs when more than one event is taking place in a system at one time and conflict occurs when a decision must be made

among alternatives. In order to evaluate the performance of computer systems including such things as waiting times and throughputs, the time parameter is added to the P-T Net model.

Progress in FY83: During the past year, the work on modeling and analyzing computer systems using Timed P-T Nets was continued. This included the development of new methods for determining net invariants and new models for demonstrating the dynamics of computer systems. Detailed models of computer bus control techniques and the operation of a commercial array processor were constructed. These models were analyzed using a method that was developed for evaluating computer system performance with Timed P-T Net models. The results of this work demonstrate how the allocation of the resources of a computer system determine its performance for a given application.

The development of the state variable P-T Net model of the interconnection of two or more microprocessors with input and output devices was continued. In particular, the structure was analyzed of the matrices used to represent this model. This model can be used to determine the avoidance of deadlock and the maintenance of throughput in multiple microprocessor systems.

Proposed Course: The work on using Timed P-T Net models for evaluating computer system performance will be continued, including the derivation of more relationships among net variables based on the structure of these nets and the refinement of the tools and models already developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE		PROJECT NUMBER
NOTICE OF INTRAMURAL RESEARCH PROJECT		20-1-100102-01 CSL
PERIOD COVERED		
October 1, 1981 to September 30, 1983		
TITLE OF PROJECT AND objectives or aim. (This must fit on one line before the funding)		
Verbal Access to Computers for the Blind		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages)		
(Name, title, laboratory, and multiple affiliations)		
David C. Songco, Electronics Engineer, CSL, DCRT		
COOPERATING UNITS (if any):		
CSL, DCRT; S.I. Allen, M.D., Medical Research Analyst, IVR, NEI; L.M. Hjeltneland, Ph.D., Expert.		
LAB BRANCH		
Computer Systems Laboratory		
SECTION		
Project Development Section		
INSTITUTE AND LOCATION		
DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANHOURS	TECHNICAL	OTHER
0.2	0.2	

Verbal Access to Computers for the Blind

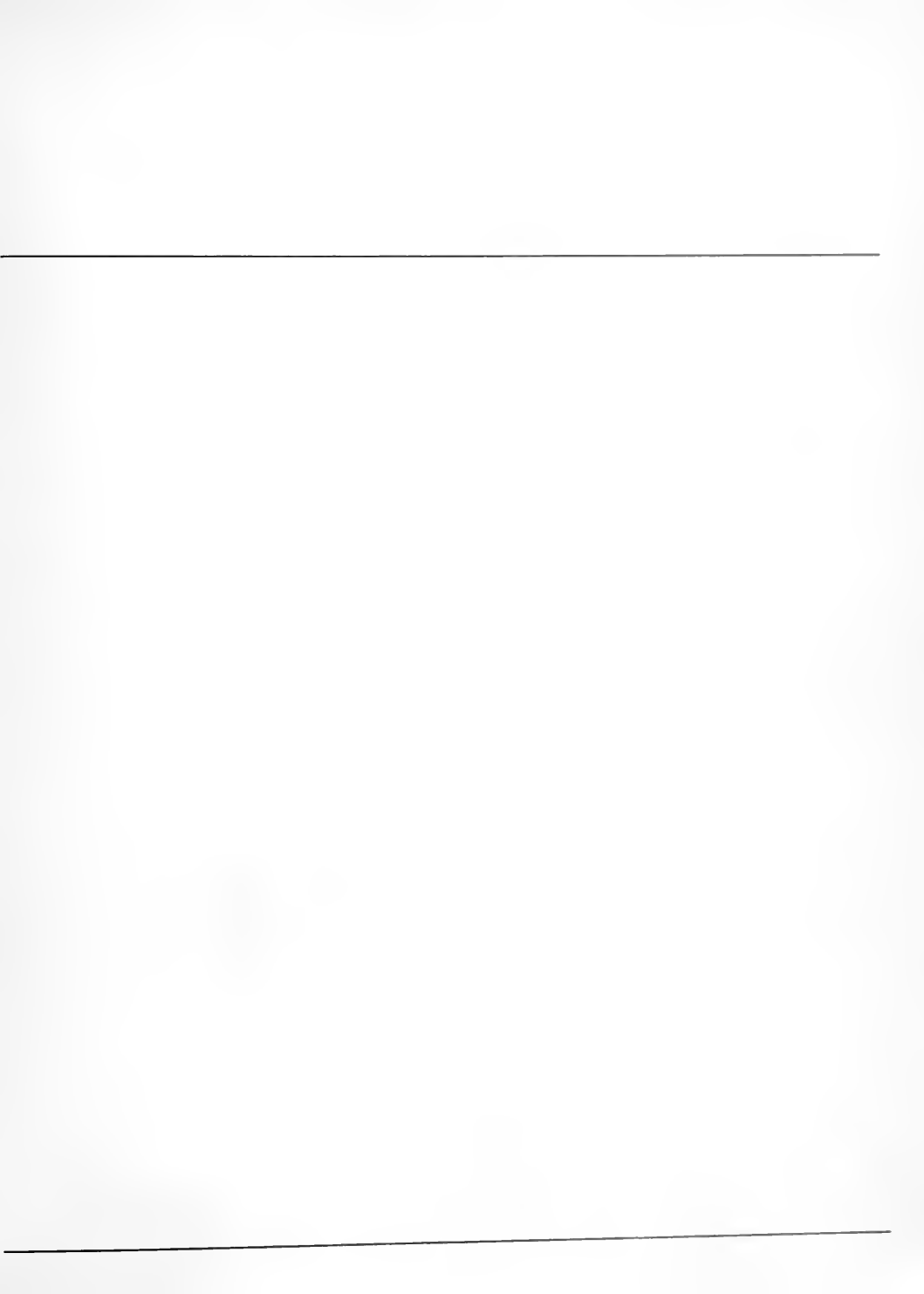
Several years ago, CSL developed a voice output terminal for the blind. This device can produce unlimited full word English speech in place of a visual CRT display. The visually impaired user can access computer systems independent of sighted assistance. This year, the CSL provided a voice output terminal to a blind scientist in NEI. The terminal design was upgraded to produce more intelligible speech with an increased speed rate output control from 50 to 750 words/minute. A means of providing voice output from analytical laboratory instrumentation is being developed, as is a voice output attachment for the DCRT-supported personal computer workstation.

Background and Objectives: In 1978, CSL developed a prototype voice output terminal for use by the visually impaired. This device has been refined in subsequent years and has been made available to a number of blind Federal employees. The goal of this project is to apply current speech synthesis technology to provide computer access for the blind.

Progress in FY83: This year, CSL began collaborating with a scientist in the NEI. A voice output terminal was provided to permit access to the DCRT Central Facility. This device utilized the Votrax VSB phoneme synthesizer, which is capable of producing full word English speech at a rate from 50 to 750 words/minute. The text to speech program is stored in 24K of read-only memory and is controlled by an Intel 8080 microprocessor.

Proposed Course: Plans are underway to provide verbal output from laboratory instrumentation. In this manner, the blind scientist will be able to operate equipment in a manner similar to his sighted colleagues. We are also

developing a voice output attachment for the IBM Personal Computer. This will extend the availability of the DCRT-supported personal workstation to blind users.



CLINICALSUPPORTCARDIOLOGY/HEARTSURGERY
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GEMENTSYSTEMAPPLIEDSYSTEMSPROGRAMMIN
PLICATIONSDATAMANAGEMENTSYSTEMSDATAB
MMINGSYSTEMSDESIGNINFORMATIONPROCESSII

Data Management Branch

J. Emmett Ward, Chief

Clinical Research, Patient Care, Epidemiology

Clinical Information Utility. During this past fiscal year the Clinical Support Section has made a number of enhancements and modifications to the Clinical Information Utility (CIU):

- Four access paths were added to the CIU system.
- The CIU data base was moved to the Mass Storage System.
- Medications, vital signs and blood bank data were added to the CIU data base.
- Software has been designed and developed that integrates retrievals.
- A system was designed and developed to automatically submit continuing retrievals, i.e., those that are submitted weekly, monthly, quarterly or a specified number of days. This extends last year's capability to obtain online schedules from users of the CIU.

BRIGHT STAT-PACK. Brian Cole (DMB/SAS); David Rodbard, Peter Munson (NICHD/BES); Jay Shapiro (CC). A computer system was developed on the DECsystem-10 that enables Clinical Center investigators to analyze their own clinical data. The major effort this year has been the development of a general regression package with such advanced features as automatic model selection, automatic weighting, and residuals analysis. Other additions to the system included programs for statistics, graphing, and data manipulation. Still in development are programs for chi-squared contingency tables, bivariate Gaussians and confidence ellipses, and linear regression with errors in X and Y.

PET-Scans, Image Tape. Sigurd Knisley, Mary Lee Dante (DMB/SAS); Rodney Brooks (NINCDS/SNB). Tapes were processed with images from the PET-Scanner augmented by information computed on a Data General computer. A program for reducing the number of image points from 16K to 300 was developed, and the resulting data was delivered to NINCDS for SAS analysis.

Seasonality Study. Judy Mahaffey, Dennis George (DMS/ASPS); Norman Rosenthal (NIMH/CPB). This system is being developed to systemize the collection and storage of data for research analysis to define the syndrome of seasonal depression. The data base will be used in analytical studies to determine interactions between environment and climate variations with mood variations. The system will serve as a model for data handling for other psychiatric studies now in progress, e.g., premenstrual syndrome. Mark sense forms were designed to collect patient data. These forms will be used for all inpatient studies in the Clinical Psychology Branch. The NCS 7001 Optical Mark Reader will be used to facilitate the data collection and storage processes.

Survival System. Diane Feskanich (DMB/SAS); Ardyce Asire (NCI). This life table analysis system originally was developed in the 1960's to support the End Results in Cancer studies of NCI. Maintenance and improvement of the system is now the primary goal. The system has been sent to tumor registries and hospitals both in the U. S. and elsewhere. During FY83 a copy of the system was sent to the Central Tumor Registry of the University of California, Los Angeles. A number of changes were made this year, including expansion of the system to handle up to 20 rate tables.

Prevalence of Major Neurological Diseases--Nigeria. Mary Lee Dante, Richard Moore (DMB/SAS); Bruce Schoenberg (NINCDS/NS); Dr. Osuntokun (U. of Ibadan). This WHO-sponsored study consists of four parts: census and health screen, evaluation of risk factors, neurological exam results, and followup. A pilot study for the census and health screen was done to determine validity and usefulness of questions and goodness of the questionnaire. During FY83 the more than 50,000 census forms were shipped to Bethesda from Ibadan. The data were keyed, edited, and corrected.

Antibody Panel Construction Program. George Roberts (DMB/SAS); James Aubuchon (CC/BB). A system was developed to construct panels of ascending statistical utility from the file of blood donor phenotypes. Panels were ranked on ability to distinguish common antibodies and to achieve desired

p-values for each antigen. The ranking scheme will be readjusted as results of the program are evaluated.

Evaluation of Physician Awareness of Pediatric Oncology Programs. Diane Feskanich (DMB/SAS); Kay Robichand (NCI/DCT). In order to trace the children referred to NCI and to determine which states/cities/doctors are aware of and use the NCI program, information is abstracted from the Clinical Information Utility and fed into programs that produce lists by state and city for each patient and each referring physician in the Pediatric Oncology Branch. Counts by year of the number of patients referred from each state are produced.

NCHS Neurological Causes of Death. Diane Feskanich, Mary Lee Dante (DMB/SAS); Nadir Bharucha (NINCDS/NS). The National Center for Health Statistics recently released multiple cause of death tapes for the just under two million people a year who died in the U. S. between 1968 and 1978. Records for all persons who had a neurological disease as either an underlying cause of death or an associated condition during the period 1971-1978 were extracted from the tapes. Tables of underlying cause by associated condition were broken down by age group, sex, and race for each year and for all years combined and were run. Age-adjusted rate tables and plots were produced for all disease categories.

Combined Cardiology/Heart Surgery Data System. Larry Martin (DMB/ASPS); Roger Dailey (DMB/DBAS); C. McIntosh, D. Rosing (NHLBI). This combined system provides a chronological record of the medical activity of NHLBI Cardiology and Heart Surgery Branch patients. Efforts on this system now are directed toward update, maintenance, ad hoc reports, and statistical analyses. This is an ongoing effort that supports NHLBI researchers.

Animal Heart Valve Replacement System. Larry Martin (DMB/ASPS); Michael Jones (NHLBI). The purpose of the system is to collect, store, and retrieve information on experimental heart valves implanted in laboratory animals. The system became operational during FY83.

Sleep Study System. Darius Georg, Peter Basa (DMB/ASPS); Christian Gillin (NIMH/BPE). This system is being developed to provide a computerized method for scoring sleep data. Programs to edit, update, and report on the data have been written and now are being implemented by Mr. Wallace Duncan and staff in the National Institute of Mental Health. The project's current emphasis is on developing more reporting options and new data transfer capabilities that will allow this data to be used in other ongoing sleep study systems within the Clinical Psychobiology Branch.

Analysis of SLE Nephritis Patient Data. George Shakarji (DMB/OC); John Klippel (NIADDK). This system to store chemistry and therapy data on all SLE (Systemic Lupus Erythematosus) patients continues to undergo modifications that will make it possible to accept more versatile therapy data. To date, this system has been used extensively to store more information on ongoing tests with multiple entries for all tests. The retrieval system also has been modified to permit general-purpose use. Subsets of the stored SLE data base are being used extensively in analytical studies to forecast critical conditions among patients.

Evaluating of Personal Characteristics and Training of Grant Recipients. George Shakarji (DMB/OC); Stewart Wright (DRG). The purpose of this study is to examine the personal characteristics and training of all of the principal investigators who were awarded their first grant in FY72, and to relate these to their subsequent success at NIH through FY80. The first step in the analysis is descriptive, involving the production of:

- a set of frequency tables (if the variable is categorical) or a set of descriptive statistics (if the variable is continuous);
- a set of two-way tables (with chi-squares for categorical variables and t-tests for continuous variables) that contain all possible pairs of variables (e.g., sex by age, B/I/D of training, degree; age by B/I/D of training, degree, etc., for all other personal, training, and success variables); and
- for categorical variables only, compression of tables where required by unsatisfactory chi-square results (too many low-frequency or zero calls).

The first step of the analysis is complete. The second step, which is underway, involves the selection and use of multivariate analyses to determine the weights of appropriate variables of training and personal characteristics with respect to measures of success.

Evaluation of SLE Test Data. Dave VanSant, George Shakarji (DMB/OC); E. K. Harris, (DCRT/LAS); John Klippel (NIADDK). This study is designed to see if the doubling of an SLE (Systemic Lupus Erythematosus) patient's creatinine results can be predicted by changes in other blood chemistry measurements. The doubling of serum creatinine in patients with SLE nephritis often signals the onset of a severe phase in the disease. Discriminant functions were computed from data on a subset of matched patients; some for whom creatinine had doubled, others in a less advanced stage of the illness. The functions were then applied to serial data on all patients in the study in an attempt to see how well the doubling of creatinine could be predicted. Results were encouraging, but the need is evident for a larger input data set to the discriminant function program.

Arthritis and Rheumatism Branch Outpatient Computer Scheduling System. David VanSant, George Shakarji (DMB/OC); Dr. Austin, Dr. Klippel (NIADDK). A computer package has been implemented for the scheduling of SLE patients. For each SLE (Systemic Lupus Erythematosus) nephritis patient, a schedule is derived, based on the category of the patient's classification and admission date, and the various procedures and tests to be administered to the patient for the following month. Provisions are made for changes in classification and procedures during the course of the protocol.

Dyslipidemia Computerized Recordkeeping System. George Roberts (DMB/SAS); Ernst Schaefer, Kent Bailey (NHLBI/DMB). The Dyslipidemia system continues to maintain and update its patient data file. The original analysis indicated neomycin contributed to cholesterol lowering. A second SAS data base was created for analysis of the effect of niacin on cholesterol.

Penicillin Study. Charles Twigg (DMB/ASPS); Dorothy Sogn (DIR/NIAD). A computerized system to assist in

the establishment of standard procedures for penicillin allergy determination/verification has been developed. It collects data and produces reports from the clinical trials of skin testing with major and minor penicillin derivatives in hospitalized adults. Initial analysis and design was completed during the year, and the system is being implemented. Additional reporting capabilities have now been defined and are being programmed.

Laboratory Investigation

Laboratory Inventory System. Diane Feskanich (DMB/SAS); Robert Williams (NICHD/PRB). Blood samples of the monkeys in the research colony are routinely sent from the Pregnancy Research Branch to Hazelton Laboratories for analysis. A system of command procedures was created to keep track of blood samples sent and test results returned. At Hazelton, the system creates work protocols for the lab technicians. The system can be queried at any time by either PRB or Hazelton to report outstanding tests, test results, or new tests.

Molecular Modeling. Sigurd Knisley (DMB/SAS). During FY83 Mr. Knisley continued work on modifications to the shaded surface molecular display developed by Richard Feldmann and Tom Porter of DCRT. Three-dimensionality has been further enhanced by the addition of reflection highlighting on the spheres, and transparency options have been increased thus allowing more versatile applications. A computer image of the surface binding mechanism on a mouse antibody protein was produced for Dr. Potter (NCI) for use in an article to be submitted for publication.

Seroepidemiology Data Processing System. Judy Mahaffey (DMB/ASPS); Paul Levine (NCI). The Clinical Studies Section, NCI Laboratory of Viral Carcinogenesis, is trying to find characteristics of serum samples that can be used to predict cancer. To this end, a computer system has been designed to manage all data necessary for efficient inventory control, test results feedback, and statistical analysis. The system is now operational and reports from the system are being sent to collaborating scientists in the U.S., Ghana, Greenland, and Singapore. During the past year a new

contractor took over the running of this system. DMB provided assistance in setting them up to run the system correctly.

Detection of Outliers. David VanSant (DMB/OC); E. K. Harris (DCRT/LAS). This project involves an exploration of outlier detection methods using clinical chemistry data. An outlier can easily inflate an estimated standard deviation so that its presence cannot easily be detected by rejecting observations that are more than three standard deviations from the mean. A program has been written that uses a method of Downton to estimate the standard deviation in such a way that outliers can be more readily detected. The program is currently being used for outlier detection in chemistry data from the University of Virginia.

Partial Differential Equation Solver. David VanSant (DMB/OC); Warren Piver (NIEHS). This project involves the maintenance of a partial differential equation solving program on the IBM System 370. The program is a product of International Mathematical and Statistical Libraries, Inc., and is leased from IMSL by the investigator. At the investigator's request, a new version of the program offering improved convergence properties was obtained from IMSL and implemented in 1983. This system is an easy-to-use finite element program that solves a large class of elliptic (steady state), parabolic (time-dependent) and eigenvalue partial differential equation problems in general two-dimensional regions. It has a preprocessor program that allows a user to supply the problem description in a greatly simplified form so that no knowledge of FORTRAN is required. Graphical output can also be produced; scalar, vector and stress fields can be displayed via the Calcomp plotter. We will keep this job active a while longer just to ascertain that it is completely debugged.

Program Management and Administration

Administrative Data Base (ADB). Marvin Katz, Ron Wicks (DMB). This ongoing project utilizes data base technology in support of NIH-wide materiel and financial management activities. As the Materiel Management System (MMS) entered its fifth year of

development and operation, much time was spent in enhancing existing software. During FY83 some 99 change control items successfully went into production. The following are several new developmental efforts that were also implemented:

- The design and development of the Stock Requisitioning, and the central stores and self service stores inventories; development of new central procurement software; and implementation of comprehensive cash management procedures. New procurement software and cash management procedures were both implemented during May 1983.
- The development of the Financial Management System (FMS). Personnel from the American Management System (AMS), the Division of Financial Management (DFM), and DCRT cooperated in a joint review of the detailed document design and functional description of the new FMS, which was enlarged to include open document processing as well as fund certification, fund control, and general ledger modules.
- We continue to maintain the NIH Central Accounting System. New DHHS requirements concerning audit disallowances made it necessary to change the effect of five accounting transactions being used by CAS and to add six new transactions. We had to modify the tables that drive the CAS, the master file update programs, and the effected report programs. This major project had to be coordinated with DFM, DCRT, and other users of the CAS.

Management/Service and Supply Fund System. A. Kelly, R. Edwards, R. W. Edwards, W. Vincent (DMB/CSS); S. George (DFM). The Clinical Support Section designed and developed a retrieval and reporting system for the Division of Financial Management that produces financial statements for both the Management Fund and the Service and Supply Fund. This system, which runs both in batch and interactive modes, is used by DFM accountants to monitor its assigned accounts and to produce monthly, quarterly, and annual reports for the B/I/D's. Additionally, DFM can use the system to answer specific questions concerning NIH accounts.

Full-Time Equivalency. Mike Letke (DMB/ASPS), George Roberts (DMB/SAS); John Hartinger (NCI/FMB). This system for monitoring the ceiling levels and full-time equivalency many years for NIH was built in FY82. During FY83 straight line and accession/separation year-end projections were added to the ceiling reports, and special experts were combined with NIH consultants/experts.

Freedom of Information Act System. Dennis George (DMB/ASPA); Nancy Cherry (NHLBI). This system tracks FOIA requests from receipt through completion and provides reports giving hours of work and costs incurred in responding to FOIA requests. Analysis and design have been completed, and the system currently is being implemented.

NIH Nutrition Grants Monitoring System. Judy Mahaffey (DMB/ASPS); Thomas Vogl (OD). A system has been designed for the NIH Nutrition Coordinating Committee to assist them in monitoring and reporting data on biomedical and behavioral nutrition research at NIH and at other agencies within DHHS. The system is operational and Dr. Vogl's office is currently using it to answer inquiries from NIH directors' offices, the White House, Congress, and the public as they relate to dollar amounts and percentages of grant money being spent in the area of nutrition. This is an ongoing project with the data base being created each fiscal year. During FY83 work was started to involve all government (nutrition) grants under a new system that will be developed by DMB/ASPS.

OHMO Health Delivery Registry. George Roberts (DMB/SAS); Mike Mock (DHHS/OHMO). The Office of Health Maintenance Organizations must watch the financing needs of the prepaid health units it oversees with the financing capabilities of investors such as insurance companies. Mr. Roberts wrote programs to combine capability and financing needs information, and provided update, search, and report capabilities.

NCI, RAEB Grants/Contracts Information System (GENIUS). Penny Brogan (DMB/ASPS); Harry Canter (NCI). The Grants Elemental Network Internal Users System (GENIUS), operated by the Research Analysis and Evaluation Branch of DEA, NCI, is the official NCI programmatic information system. The system, initiated

in 1973, has been enlarged and maintained in an ongoing fashion. It provides both administrative and scientific classifying information via five subsystems: grants, contracts, intramural projects, unfunded grants, and grant-supported literature. The grants and contracts systems are "generalized" so they can provide information for any NIH Institute. Most of the work done this year involved modifying existing software and expanding individual files to accommodate new data elements. Enhancements include: calculation of expenditure percentages by subject area, simplification of query formulation with the use of a WYLBUR command procedure, and interfacing GENIUS with the NIH nutrition system.

NIAID Intramural Reporting System. Dennis George (DMB/ASPS); Jeffrey Schriver (DMB/DBAS); K. Sells (NIAID/IRP). This project, designed and implemented this year, provides NIAID with a weekly analysis of actual monies expended versus budgeted amounts. A fiscal year master file is updated weekly using obligations and commitment transactions posted to the NIH Central Accounting System. Five reports display data that includes CAN, Object Class, Cost Center, and budgeted amounts.

Visiting International Scientists in America MIS (VISA). Penny Brogan (DMB/ASPS); Libby Low (FIC). A total revision has been made to the foreign scientists management information system used by the Fogarty International Center. This system provides information on foreign scientists who are in the U. S. to perform health research. Most of these scientists are working at NIH. The revised system now provides more complete current information on each scientist. It also provides more accurate editing and updating capabilities at time of data entry and produces new reports. Important new features include:

1. the use of microfiche to facilitate telephone inquiry responses;
2. ad hoc querying of the data base, now expedited by combining parameterized COBOL programs with QUIKJOB;
3. 24-hour turnaround for producing annual reports that formerly required two months to compile;

4. automatic notification of such things as impending terminations and expiration of I-94 dates (which now expedites FIC staff's ability to take appropriate actions); and
5. the capability to post "across the board" pay changes.

Employee Health System and Accident Reporting (CASE) Reports. Darius Georg (DMB/ASPS); Julio Rivera, John Leach (ORS/S). A system has been developed to combine the employee health and accident reporting systems. The system was implemented and turned over to the users during FY83.

Committee on Academic Science and Engineering (CASE) Reports. Darius Georg (DMB/ASPS); J. Bailey (OD/OPPE). This project involves a broad spectrum of data processing support required for the collection and reporting of DHHS Obligations to institutes of higher education, research and development centers, and nonprofit institutions. This is an ongoing project.

Training Information System. John Parks (DMB/ASPS); Ursula Lohman (OPM). This system was developed to help the Training Management Branch expedite data requests and management analysis of data gathered on DHHS Form 350. Programming is complete. The system test, documentation, and user training are underway.

System for Controlling and Monitoring Complaints of Discrimination at NIH. Darius Georg (DMB/ASPS); G. Yee, M. Williams (OD/DEO). This project establishes and maintains a file that provides statistical data, on a case-by-case basis, of formal and informal complaints of discrimination at NIH. In the past year Mr. Georg revised and simplified the retrieval process.

System for Classifying NIH Research and Development Awards. Darius Georg (DMB/ASPS); William Rhode (OPPE/RA). The objective of this ongoing project is to test the feasibility of using CRISP index terms for categorizing NIH research projects into basic, applied, or developmental research and then to develop a computer system to show percentage distribution of dollars associated with each category. New methods were tested this year to index the CRISP terms in order to develop a more precise percentage of

distribution for each area of research. Once a feasible system is developed, the data collected, analyzed, and compiled by the system will be used to prepare annual reports to the Office of Management and Budget (OMB) and the National Science Foundation (NSF).

DCRT Computerized Bibliography. Richard Baxter (DMB/OC); Karen Griffin, Patricia Miller (DCRT/OD). This project, complete this year, was begun in FY79 to create a file of citations for all papers published by DCRT authors. It is now possible to retrieve bibliographic reports from the file.

Interferon Production Monitoring System. Dennis George (DMB/ASPS); Hilton Levy (NIAID/LVD). The purpose of this project is to develop a system to monitor the production and subsequent use of interferon on an experimental basis. Various production techniques and use protocols are to be monitored in both human and animal subjects. Analysis and design have been completed and implementation of the system has been started.

Information System of Extramural Scientists. Darius Georg (DMB/ASPS); William Rhode (OD/OPPE). This project involves the creation of a data base drawn from various sources to perform analysis of patterns of involvement in NIH science review activities by extramural scientists. The data base has been created and reports are being run as requested. During FY83 the system was modified to provide online editing and also to create history files for data from 1950 through 1978.

Medical Records Auditing System. Judy Mahaffey (DMB/ASPS); Gloria Burich (CC/MRD). The purpose of this system is to assist the Medical Records Department in the monitoring and reporting of the status of medical records from the time they enter the department until they leave. The audit segment of the system was completed during the past year. Now being explored is the possible further automating of data transmissions directly from their data transcription contractor in Florida. Also being considered is more sophisticated scanner equipment.

AIRS Personnel System. Steve Soroka (DMB/ASPS); L. Lee Manuel (DCRT/OD). This project involves a

complete revision of the system due to the availability of the new TAPS file. Analysis, design, and implementation were completed during the last year.

Biomedical Communications Applications

Selective Dissemination of Information. Sigurd Knisley (DMB/SAS). The Scientific Applications Section has continued its support of the current awareness search for both Chemical Biological Activities (CBAC) and Biosciences Information System (BIOSIS). Retrospective searches are referred to the NIH Library staff. In the spring of 1983 a study was done to determine the utility of this service at NIH and to explore a personal computer-based system as an alternative.

Bibliographic Data Base. Sigurd Knisley (DMB/SAS); Curtis Harris (NCI/DCCP). Bibliographic information and keywords drawn from Dr. Harris' reprints of scientific articles were entered into the computer files. A system for searching this information and printing it for direct inclusion into book and journal bibliographies was set up using the powerful new tools available in WYLBUR.

Computer Research and Technique Development

SFOR (Structured FORTRAN) Compiler. Bob Magnuson (DMB/OC). The SFOR compiler, which generates block-structured IBM FORTRAN source code, was further enhanced to assist programmers writing structured programs. There are six different kinds of blocks available to the FORTRAN programmer--CASENTRY, FOR, IF, LOOP, REPEAT, and WHILE.

RMAG Products Support. Bob Magnuson (DMB/OC). Necessary support is provided for RMAG, SLR, Logic Subroutines, Arithmetic Subroutine, SLANG, Voice Input, PDOC, CP Tools, and SFOR. This ongoing support includes software maintenance, customer assistance, and the teaching of formal DCRT courses on the use of these products. In particular, a special effort had to be mounted to change over to the new WYLBUR format data sets.

PDOC: Program Documentation System. Bob Magnuson (DMB/OC). PDOC is a tool used to document programs. It is a front end to the WYLBUR Document Formatter, allowing the users to employ all of the Document Formatter's powerful features while adding several useful enhancements of its own. PDOC was enhanced during the past year in order to better produce the large and complex *MLAB Beginners Guide*. A number of PDOC commands have been revised and new ones have been added to enable the author of a document to customize formatting and to make insertions, deletions, or rearrangements of screen lines at will with the references in the author's text being automatically revised by PDOC. Another new feature of the system enables the author to "reproduce" in the document a boxed version of a CRT screen display and then to reference each line within the box symbolically in text discussion.

CP Tools. Bob Magnuson (DMB/OC). CP Tools is an integrated set of WYLBUR command procedures that permits the user to issue single user-defined commands to expedite text entry/editing and running jobs while on the NIH7000 terminal. Among the new tools developed during the year are: "token editing" for changing variables or keywords without affecting other parts having identical substrings; JCL generators for microficheing any number of hold jobs and for running SLANG and SFOR; and getting PF keys on the NIH7000 to do whatever the user wants.

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Computer Center Branch

Joseph D. Naughton, Chief

New Facilities

A policy decision to facilitate microcomputer access to resources and services available on the Computer Utility led to the implementation of two functions: terminal emulation, a means to allow microcomputers to be used as terminals to access the mainframe computers; and file transfer, a system for transferring programs and data from the microcomputer to the mainframe computer (called "uploading") and from the mainframe computer to the microcomputer ("downloading").

Microcomputer-based devices that are ASCII (American Standard Code for Information Interchange) teletype-compatible can access both the IBM System 370 and the DECsystem-10 over the switched telephone network using the ASCII communications code. The file transfer function required the use of a packet-based protocol with companion programs that run simultaneously on both the mainframe computer and the microcomputer. Extensive testing was done to ensure that the communications packages selected would provide reliable and accurate data transfer services on both the IBM System 370 and the DECsystem-10, while meeting the specific requirements of the Utility's user community.

An entirely new communications service was implemented on the IBM System 370 to provide switched network access to users with 3270-type display devices or microcomputers. The new service, called System Network Architecture (SNA) Synchronous Data Link Control (SDLC), allows users of microcomputers that can emulate the 3270 protocol to use IMS, TSO, or WYBLUR under TSO without incurring the cost of a leased telephone line.

Up-to-date status information about online data sets, migrated data sets, and dedicated volumes has been placed online, and users now receive this information at their convenience through the terminal. This capability frees Computer Center personnel from the responsibility of creating quickly-outdated paper reports, and allows them to devote more of their time to more critical user needs.

The Tektronix graphics package was added to SPEAKEASY, greatly increasing the usefulness of this language. Users can use the package to obtain high quality plots of data in a matter of seconds. Ease of use is a major feature of the SPEAKEASY graphics package. Once results have been calculated, a plot may be generated on a Tektronix terminal using as few as two SPEAKEASY commands.

Full color graphics capabilities were made available through OMNIGRAPH on the DECsystem-10. Eight standard colors and as many as 256 user-defined color combinations can be used for producing multicolor graphs or colorful visuals in MLAB or POSTER.

Because TELL-A-GRAF and DISSPLA have replaced the Integrated Plotting Package (IPP), and maintenance and support for the system were discontinued by the original author, plans were developed to phase IPP out of service. A function to allow users to produce printer plots directly using DISSPLA is being implemented so that IPP can be retired without inconvenience to users.

Customer Assistance and Systems Maintenance

Customer assistance continued to be an important priority for the Computer Center during FY83. The Programmer Assistance and Liaison Unit, which has continued to operate under restricted hours for telephone and drop-in help, recorded 20,100 calls or visits from customers needing assistance this year. In addition, 2,800 Programmer Trouble Reports were researched and answered.

SYSGENS installed during the past year numbered 75. Nearly 9,000 "fixes," both preventive and corrective, were tested and applied to the system, and 12 new releases of current software packages were installed.

User Training

Alternative training opportunities were emphasized this year in order to meet the challenge of providing adequate user training. 5,214 requests for training were received this year and 2,939 students were accommodated in 150 sessions of 57 different courses.

Two distinct means of individual self-study were available for those who could not be accommodated in the formal training program:

- Multimedia self-study courses, available on a loan basis on a variety of topics and a wide range of levels, allow students to learn from texts, workbooks, and audio or video cassettes. A new self-study course, "Creating an OS/VS Program," was acquired and introduced this year, bringing the total number of courses available to 27. Over 750 students utilized these multimedia courses during FY83.
- Independent Training Assisted by Computer (ABC)--a hands-on, computer-assisted approach--was implemented this year to supplement the multimedia self-study program that was introduced in past years.

ABC allows students to study at their own pace, using a printed text or the computer terminal. Interactive review lessons and practice exercises encourage hands-on experience. ABC courses are an ideal alternative for students who need to review a topic or who cannot travel to NIH for classroom training.

"Introduction to WYLBUR" was the first ABC course made available this year, because a knowledge of WYLBUR is fundamental to the effective use of the NIH Computer Utility and there is always a backlog of students for basic WYLBUR courses. ABC "Introduction to WYLBUR" consists of 40 short lessons that cover the same information as two elementary WYLBUR classroom courses. Over 3,000 students utilized the course this year.

Documentation and Publications

INTERFACE continued to be a particularly important source of up-to-date documentation on new hardware installations, system enhancements, and software developments. Seven issues, including the annual index, were published during the past year.

The publication won second prize in the 1982 newsletter contest conducted by the Association for Computer Machinery (ACM) Special Interest Group on University and College Computing Services. The competition involved newsletter entries from 57 academic, commercial, and research organizations,

which were evaluated based on quality of articles, organization, content, graphic design, and typography.

Five updates of the Computer Center's *User's Guide* were issued during the year. Eight new technical documents were published and 11 others were either revised or updated during the year.

Research Projects

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00113-01 CCB
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Design and Development of an Advanced Molecular Graphics Facility		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Richard J. Feldmann, Computer Specialist, CCB, DCRT		
COOPERATING UNITS (if any)		
LABORATORY Computer Center Branch		
SECTION		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.9	PROFESSIONAL 0.5	OTHER

Design and Development of an Advanced Molecular Graphics Facility

This research work deals with advances in computer technology that offer new, surprising, and powerful opportunities for improving the ability to model the structure of macromolecules. Molecular modeling can be roughly divided into three parts: getting the pieces together, getting the correct shape of the molecule, and producing pictures of the resulting molecule.

We have used centralized timesharing machines for the past fifteen years to do the first function. The evolution of desk-top work stations makes it possible to bring this molecule construction process closer to the scientist-user. The evolution of powerful array processors makes it possible to speed up and enhance the process of finding the optimal shape of the molecule being modeled. The evolution of new displays makes it possible to make representations of complex molecular assemblies, viruses, cellular components, and cells.

We have begun the design and implementation of a molecular graphics facility that will hopefully allow us to

begin to consider the question of the design of macromolecules.

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Office of the Director

Arnold W. Pratt, M.D., Director

Research Projects

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER
		Z01 CTD0110-01 00
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (40 characters or less. This must fit on one line between the hyphens) Personal Computer Workstations		
PRINCIPAL INVESTIGATOR (Last other professional personnel on exchange must appear) (Name, title, laboratory, and institute affiliation) Arnold W. Pratt, M.D.		
COOPERATING UNITS (if any) DCRT: B. McLaughlin, OD J. Dickson, CCB P.E. Burke, OD R. Magnuson, DMB D. Songco, CSL J. Oberthaler, OD		
LAB BRANCH Office of the Director		
SECTION		
INSTITUTE AND LOCATION DCRT, NIN, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.5	PROFESSIONAL 0.5	OTHER

Personal Computer Workstations

This project will apply personal computers to a variety of problems in offices and laboratories throughout NIH. The goal of this project is to determine how effectively programmable workstations can be used to perform a number of functions, including text processing, production of business and scientific graphics, maintenance and inquiry of small data files, and so forth. Use of commercial software and communications with the central NIH computer facility are being stressed.

In the first phase of the project, begun in FY83, a number of workstations, based on the IBM Personal Computer, are being installed in DCRT branches and laboratories. These computers are being used by DCRT technical and administrative personnel to evaluate the workstations from both systems and application viewpoints. A byproduct of this early evaluation will be to define the best use of available DCRT resources in promoting effective use of personal computers throughout NIH.

Multi-function Microprocessor Interface. A. Pratt (OD); D. Songco (CSL). Begun in FY80, this project seeks to adapt a variety of information acquisition techniques on a single microcomputer as a versatile data input/output interface for biomedical scientists and clinicians.

This work has led to an outgrowth of related developments in DCRT: an Office of the Director project on Personal Computer Workstations, and two Computer Systems Laboratory projects, the Medical Information Technology Project and the Personal Computers in Laboratory Applications project (both reported elsewhere in this volume).

Medical Linguistics. A. Pratt (OD), et al. This is a long-term project to define a set of semantic and syntactic forms that can aid in the analysis and interpretation of written medical statements.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER
		Z01 CTD0107-01 00
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (40 characters or less. This must fit on one line between the hyphens) Concordance Program		
PRINCIPAL INVESTIGATOR (Last other professional personnel on exchange must appear) (Name, title, laboratory, and institute affiliation) Paul J. Kalkowski, Computer Specialist, OD, DCRT		
COOPERATING UNITS (if any)		
LAB BRANCH Office of the Director		
SECTION		
INSTITUTE AND LOCATION DCRT, NIN, Bethesda, Maryland 20205		
TOTAL MANYEARS 0.1	PROFESSIONAL 0.1	OTHER

Concordance Program

A concordance is an index in which the words appearing in a document are entered with quotations of context. The reader who looks up a word in a concordance can use the quotations of context to decide which occurrences of the word might be of interest.

A program to produce concordances has been made available. It can produce the following types of output: a concordance in KWIC (Key-Word-In-Context) format; a concordance in KWOC (Key-Word-Out-of-Context) format; a word index; or a word frequency list. The program can accept an input data set consisting of lines entered with a text editor, each line containing a text fragment to be operated upon by the program in order to construct text fields or records. The input data can represent a continuous stream of text, like a book or journal article, or it can represent a collection of discrete text items, like those in a catalog or

bibliography. The program also can accept as input a pre-existing file of formatted records.

A number of program options have been provided: concordance lines may be sorted within indexed words; a format may be defined for KWOC output; keys may be constructed from multiple fields; words may be specified for exclusion (or inclusion); word definition may be modified, etc.

The description of input data and the specification of program parameters are made with problem-oriented statements and do not require changes to the concordance program.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00106-01 00
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) A Program for Finding Noun Phrases in English Text		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Paul J. Kalkowski, Computer Specialist, OD, DCRT		
COOPERATING UNITS (if any)		
LAB/BRANCH Office of the Director SECTION		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 0.9	PROFESSIONAL: 0.9	OTHER:

A Program for Finding Noun Phrases in English Text

A pilot program has been written to find noun phrases in English text. Potentially, such a program might be useful as a step in automatically indexing text or in performing information retrieval from English language data bases.

In general, the program executes as follows: Each word of text is looked up in a dictionary containing at present about 27,000 words and phrases. If found, part of speech possibilities are taken from the dictionary entry. If not found, the word is examined for prefixes, suffixes, and inflectional endings, and an attempt is made to derive the word from a word in the dictionary. A part of speech may be deduced from a suffix, an inflectional ending, and/or properties of a base word. Otherwise, an unknown word is assumed to be a noun. Each word of text is then considered in its context and

with its possible parts of speech, and rules of syntax are applied to determine an actual part of speech, or else to reduce the part of speech possibilities. When a sentence is complete, the program scans it for possible noun phrases.

The program is not based upon any mathematical model of language, and it does not produce a complete parse of a sentence showing all relationships between words. Problems encountered by conventional parsers are avoided (e.g., resolving ambiguity, determining antecedents of pronouns), and indeed are considered irrelevant to the program's goal of finding noun phrases.

Because the program cannot always determine a word's part of speech, the program cannot find noun phrases exactly, and it is designed to err on the side of finding noun phrases that are too long. In any system that employs the program, it is anticipated that subsequent steps could be taken to refine the noun phrases that are produced.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00040-05 00
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Actin Assembly in Nonmuscle Cells		
PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.) (Name, title, laboratory, and institute affiliation) Stephen L. Brenner, Research Chemist, OD, DCRT		
COOPERATING UNITS (if any) Laboratory of Cell Biology, NHLBI		
LAB/BRANCH Office of the Director SECTION		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MANYEARS: 1.0	PROFESSIONAL: 1.0	OTHER:

Actin Assembly in Nonmuscle Cells

The protein actin is a major cytoskeletal component of all eukaryotic cells, serving both structural and motility-related roles. In the cell, assembly and disassembly of actin microfilaments are temporally and spatially regulated. This project is aimed at understanding the mechanism of G-actin assembly into F-actin, the role of the hydrolysis of actin-bound ATP, and the cellular control mechanisms for actin assembly.

This past year we have shown that monomer-polymer subunit exchange in steady state F-actin solutions occurs by a diffusion mechanism and not by opposite-end assembly-disassembly (treadmilling). We have also discovered that F-actin alone possesses ATPase activity independent of monomer-polymer interaction; exchange of F-actin-bound ADP for ATP in solution can occur directly by a "breathing" of the polymer structure.

The assembly of F-actin with bound ADP has been studied. Even though no nucleotide hydrolysis occurs, the kinetics of assembly are consistent with a rate-limiting nucleation step followed by elongation. We have begun to measure absolute rate constant for the assembly reaction by using a chemically cross-linked actin trimer to bypass the nucleation step.

A study has begun to determine the mechanism for control of actin filament assembly in human platelets. A 1:1 complex of actin and a 90,000-dalton protein has been purified from platelets. The modulation of actin assembly by this complex is currently being investigated.

Publications:

- Brenner, S.L., and Korn, E.D.: On the mechanism of actin monomer-polymer subunit exchange at steady state. *J. Biol. Chem.* 258: 5013, 1983.
- Brenner, S.L., Tobacman, L.S., and Korn, E.D.: The kinetics of actin polymerization and monomer-polymer subunit exchange at steady state. In *Dos Remedios, D. (Ed.): Actin* (in press).
- Tobacman, L.S., Brenner, S.L., and Korn, E.D.: Effects of Acanthamoeba profilin on the pre-steady state kinetics of actin polymerization and on the concentration of F-actin at steady state. *J. Biol. Chem.* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00134-01 00
PERIOD COVERED March 1, 1981 to September 30, 1983		
TITLE OF PROJECT (25 characters or less. Title must fit on one line between the borders.) Molecular modeling of the structure of carbohydrates		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) Richard J. Feldmann, Computer Specialist, OD, DCR		
COOPERATING UNITS (if any) Dr. Michael Levitt, Dept. Chemical Phys., Weizmann Inst. of Sci., Rehovot, Israel Dr. J. David Karm, Dept. Chem., Towson State Univ., Towson, MD Dr. David H. Bing, Cambridge Research Laboratories, Cambridge, MA		
LABORATORY Office of the Director		
SECTION		
INSTITUTE AND LOCATION DCR, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.5	0.5	

Molecular modeling of the structure of carbohydrates

Many variations of the basic carbohydrate ring structure are to be found in biological systems in the form of chain and branched structures. These structures are to be found on the surfaces of cells where they serve as the elements of recognition between cells and other processes. Crystallography has been done on some of the variational units and on a few small chains. We have begun a graphics project to construct as many of the naturally occurring structures as have been reported in the literature. In order to produce realistic structures, an energy minimization program is being used to find energy-minimum and therefore stable conformations. Data from Nuclear Magnetic Resonance (NMR) experiments also will be used to help determine the shape of the carbohydrate structures. Preliminary model construction and minimization indicates that carbohydrates are rather more rigid than amino or nucleic acids. If this proves to be true in general, the shape of a complex structure will be simply, and perhaps uniquely, determined by the type and connection of the components.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00134-01 00
PERIOD COVERED October 1, 1982 to September 30, 1983		
TITLE OF PROJECT (25 characters or less. Title must fit on one line between the borders.) Reprint File Index		
PRINCIPAL INVESTIGATOR (Last other professional personnel on subsequent pages) (Name, title, laboratory, and institute affiliation) James V. Oberholzer, Acting Chief, DCR Office of ADP Policy		
COOPERATING UNITS (if any) NM, CC: Richard Margolin, M.D.		
LABORATORY Office of the Director		
SECTION Office of ADP Policy		
INSTITUTE AND LOCATION DCR, Bethesda, Maryland 20205		
TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.05	.05	

Reprint File Index

This is an experimental project to determine the potential usefulness of WYLBUR Command Procedures in building, maintaining, and searching an index of journal article reprints. A command procedure called REFILE allows the user to enter certain information about each journal article or book chapter he or she wishes to index. This information is retained in an online WYLBUR data set for later inquiry. The index

can be searched and selected references can be displayed in tabular or bibliographic citation format.

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